Effects of hypertonic saline on intracranial pressure variables in subarachnoid haemorrhage patients

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Ph.D. thesis

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"Following the intravenous injection of 30 per cent sodium chloride, the normal convexity of the brain in the trephine opening disappears soon after the injection is begun, so that the brain is seen to lie flat. As the intravenous injection of salt is continued, the brain falls away from the skull until the surface presented becomes concave. The maximum shrinkage has been observed usually in from fifteen to thirty minutes after the completion of the injection, when the brain lies flaccid, 3 to 4 mm below the inner table of the skull."

LH Weed and PS McKibben, 1919.
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<table>
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<tr>
<td>ABP</td>
<td>Arterial blood pressure</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood-brain-barrier</td>
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<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>CBV</td>
<td>Cerebral blood volume</td>
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<tr>
<td>CDO₂</td>
<td>Cerebral oxygen delivery</td>
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<tr>
<td>CI</td>
<td>Cardiac index</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>CPM</td>
<td>Central pontine myelinolysis</td>
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<tr>
<td>CPP</td>
<td>Cerebral perfusion pressure (CPP = MAP – ICP)</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CVP</td>
<td>Central venous pressure</td>
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<tr>
<td>DIND</td>
<td>Delayed ischemic neurological deficit</td>
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<tr>
<td>ELWI</td>
<td>Extravascular lung water index</td>
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<tr>
<td>EVD</td>
<td>External ventricular drain</td>
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<tr>
<td>FFT</td>
<td>Fast Fourier transformation</td>
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<tr>
<td>GCS</td>
<td>Glasgow Coma Score</td>
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<tr>
<td>GOS</td>
<td>Glasgow Outcome Score</td>
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<tr>
<td>HR</td>
<td>Heart rate</td>
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<tr>
<td>HS</td>
<td>Hypertonic saline</td>
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<tr>
<td>HSS</td>
<td>7.2% (72 mg/mL) saline in 6% (60 mg/mL) hydroxyethyl starch 200/0.5 (sodium content: 1.23 mmol/mL)</td>
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<tr>
<td>ICP</td>
<td>Intracranial pressure</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
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<td>ITBI</td>
<td>Intrathoracic blood volume index</td>
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<td>IVH</td>
<td>Intraventricular haemorrhage</td>
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<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
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<td>NS</td>
<td>Normal saline</td>
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<td>SAH</td>
<td>Subarachnoid haemorrhage</td>
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<tr>
<td>SpO₂</td>
<td>Peripheral oxygen saturation</td>
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<td>TBI</td>
<td>Traumatic brain injury</td>
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PUBLICATIONS INCLUDED IN THE THESIS

The thesis is based on the following articles, which are referred to in the text by their roman numerals:


III. Bentsen G, Stubhaug A, Eide PK. Differential effects of osmotherapy on static and pulsatile intracranial pressure (ICP). Crit Care Med; accepted for publication.
INTRODUCTION

Subarachnoid haemorrhage

Definitions, incidence, and outcome

Subarachnoid haemorrhage (SAH) is characterized by the presence of blood in the subarachnoid space; the space covering the central nervous system that normally only contains cerebrospinal fluid. The bleeding can be either traumatic or spontaneous. This thesis only deals with the spontaneous, non-traumatic bleedings, which in about 80 to 85% of the cases are due to the rupture of a cerebrovascular aneurysm (van Gijn and Rinkel, 2001).

The overall incidence of spontaneous SAH is in meta-analyses reported to be somewhere around 10:100,000 annually, but with variations from six to eight in USA and most of Europe to around 20:100,000 in Finland and Japan (Linn et al., 1996; Teunissen et al., 1996; Menghini et al., 1998; van Gijn and Rinkel, 2001). Women have a 1.6 times higher risk than men (Linn et al., 1996), and black people twice the risk of whites (Broderick et al., 1992) of experiencing a SAH. Smoking, hypertension, and alcohol abuse increase the risk for SAH (Teunissen et al., 1996).

Case fatality rates are high in SAH compared with other forms of stroke, varying between 32% and 67%, with a weighted average of 51%, but the fatality rate has decreased over the last three to four decades by 0.5 to 1.0% annually (Hop et al., 1997; Johnston et al., 1998; Koffijberg et al., 2008). Even though SAH accounts for only 3% of all strokes (Sudlow and Warlow, 1997), 4.4% of cerebrovascular deaths are due to SAH (Johnston et al., 1998). SAH also accounts for 27% of total years of potential life lost before age 65 due to cerebrovascular disease (Johnston et al., 1998). This is due to the high fatality rate and the fact that the population of SAH patients is younger than the populations with cerebral infarction and intracerebral haemorrhages.
About 50% of those who die, die within the first two days after the stroke (Stegmayr et al., 2004). This represents a challenge to the acute management of these patients. Of vital importance is prompt diagnosis, rapid transfer to a neurosurgical unit, early securing of the aneurysm, and optimal intensive care (Bakke and Lindegaard, 2007).

Of the survivors, approximately one third need lifelong care (Hop et al., 1997), and almost a half of the survivors suffer life-long cognitive impairment (Hackett and Anderson, 2000; Mayer et al., 2002). Hopefully, improved intensive care with avoidance of secondary insults can help reduce also these figures.

**Mechanisms of injury to the brain.**

Brain injury after SAH is a biphasic event.

*First* there is the initial impact of the bleeding itself causing cerebral ischemia. A sharp increase in intracranial pressure (ICP) leads to a dramatic reduction in cerebral perfusion pressure (CPP) (Talacchi, 1993). But even after recovery of CPP, there is evidence of prolonged hypoperfusion with flow measured in different studies at 20 – 80% of baseline levels (Jackowski et al., 1990; Piepgras et al., 1995; Prunell et al., 2004). There is also evidence of loss of autoregulation, disruption of the blood-brain-barrier (BBB), cellular swelling leading to cerebral oedema, and initiation of apoptotic processes, but the understanding of the underlying mechanisms and the ultimate relevance of these early changes is still incomplete (Cahill et al., 2006; Mocco et al., 2007; Schubert and Thome, 2008).

*Secondly*, given that the patient has survived the impact of the bleeding, there is a more prolonged phase. Many patients experience bleeding into the ventricular system affecting drainage of cerebrospinal fluid (CSF). This may lead to the development of hydrocephalus and subsequent rise in ICP leading to ischemia within hours (Bakke and
Lindegaard, 2007). Cellular swelling and disruption of the BBB induces cerebral oedema, which also increases ICP. This process typically culminates after two to four days (Thiex and Tsirka, 2007), but may cause distortion and displacement of brain tissue resulting in compression of vital structures (“herniation” syndromes). Claassen et al. have reported the presence of cerebral oedema to be associated with poor outcome. Global oedema was found at admission in 8% of patients with an additional 12% developing delayed oedema (Claassen et al., 2002). Reaching peak incidence at about a week, delayed vasospasm may also cause seriously impaired cerebral blood flow (CBF) and ischemia. Radiographic evidence of vasospasm can be found in more than 50% of patients, but only half of these experience symptoms of delayed ischemic neurological deficits (DIND) (Keyrouz and Diringer, 2007).

Somewhere along the time line, there is also a periprocedural phase, where the source of bleeding is secured either by surgical clipping or endovascular coiling. These procedures also carry some risk. Complications may arise due to thrombosis, bleeding, induced vasospasm, or excessive traumatisation of brain tissue (Bakke and Lindegaard, 2007).

**Aspects of treatment**

In short, the goals of treatment are; meeting the neuronal metabolic needs at all times, avoiding secondary deterioration, and avoiding further bleeds.

The avoidance of re-bleeding is achieved by surgical clipping or endovascular coiling of the aneurysm. The trend is to perform this intervention at an early stage. The risk of re-bleeding is closely related to time and the occurrence of re-bleeding is strongly associated with poor outcome (Ohkuma et al., 2001; Bakke and Lindegaard, 2007). The risk of re-bleeding is highest during the first 24 hours after the initial bleeding and immediate administration of tranexamic acid upon diagnosis of SAH may reduce the risk of early re-bleeding (Hillman et al., 2002).
Securing optimal oxygen and nutritional supply has many aspects. First, one important measure is to reduce the oxygen need. This can be achieved by avoiding hyperthermia and sedating the patient, in the final instance by inducing a pentobarbital coma. Sedation of the patient may warrant securing the airway and the institution of mechanical ventilation. Mechanical ventilation is often also needed because the patient is unconscious to begin with or because pneumonia impairs gas exchange to the degree that the patient is hypoxemic. By mechanical ventilation the oxygen supply and carbon dioxide removal can most often be well controlled. For the oxygen taken up in the lungs to be delivered to the brain we must ensure that the haemoglobin content is sufficient, and that the brain is perfused. This means that the CPP has to be adequate, and the blood pressure and cardiac output can be controlled by adequate volume supply and the use of vasoactive drugs when needed.

As is obvious from the previous section, raised ICP is often a threat to adequate perfusion and cell function. Intracranial hypertension can be attenuated by sedation, head elevation, and temperature control. For short time relief of increased ICP, reduction of arterial CO₂ content by hyperventilation can be very effective, but aggressive hyperventilation can induce grave vasoconstriction leading to ischemia in itself. Especially in patients suffering from acute hydrocephalus caused by intraventricular haemorrhage (IVH), external drainage of cerebrospinal fluid (CSF), either by a ventricular catheter or by the lumbar route is very helpful in rapidly decreasing the ICP. In extreme cases of cerebral swelling, the procedure of decompressive hemicraniectomy can be life saving (Schirmer et al., 2007; Hutchinson et al., 2007). This brings me to the subject of osmotherapy, which is the last of the commonly applied strategies used to attenuate raised ICP.
Osmotherapy

Context definition
The use of osmotically active solutions to reduce the volume of the intracranial content (Paczynski, 1997).

Mechanisms
The water content of the brain approximates 80% (Bhardwaj, 2007). When we add that a small 1.6% reduction in water content yields a 90 mL reduction in brain volume (Cascino et al., 1983), we have the foundation for understanding osmotherapy.

The osmotic pressure of a solution is proportional to the number of particles in a given volume (Rapoport, 1976), but osmotic effectiveness of solutions depends as much on the properties of the membrane(s) separating the different compartments of solutions as their respective molarities. This can be expressed as the membrane’s osmotic reflection coefficient (σ) for a given solute. Given a reflection coefficient of zero, the membrane is completely permeable for that solute. On the other hand, if the membrane is impermeable, the value is one (Zornow, 1996).

The properties of the BBB differ greatly from the properties of capillaries elsewhere in the body. Unlike “ordinary capillaries”, the BBB is virtually impermeable to small solute molecules like sodium and chloride. It is these compounds that regulate the water balance across the BBB. The importance of the colloid osmotic pressure, known from the Starling equation, is less in the uninjured brain; the flow of water is tightly controlled by the crystalloid osmotic pressure.

Another important property of the BBB, is the relative impermeability of molecules of water (Raichle et al., 1976). On 9 October 1991 the first water channel, Aquaporin-1, was discovered (Preston et al., 1992). Subsequently other aquaporins have been identified, and
Aquaporine-4 located in the brain may control most of the water transport across the BBB, and represent a rate limiting factor for this process. However, the importance of Aquaporine-4 in human cerebral oedema is still undefined, but Aquaporine-4 has a potential for future therapeutic interventions (Agre et al., 2002; Chen et al., 2007; Bloch and Manley, 2007).

The intravenous infusion of a hypertonic solution establishes an osmotic gradient between the intravascular space and the extracellular volume of the brain. This gradient provides a potent force to move water from the brain’s extra- and intracellular space into the capillaries. In this way, the volume of the brain is reduced and thereby the ICP (Zornow, 1996).

There are other theories as to how the osmotherapeutics reduce ICP. There are several variants of “haemodynamic” theories, all emphasizing the importance of dynamic changes in cerebral blood volume (CBV) (Paczynski, 1997). Muizelaar et al. have reported, from a study in cats, a rapid reduction in the diameter of arterioles and venules on the surface of the brain immediately after an intravenous mannitol bolus of 1 g/kg given during 1 minute (Muizelaar et al., 1983). Subsequently they reported how this effect on ICP was greater in patients with intact autoregulation, than in patients without (Muizelaar et al., 1984). I must, however, express methodological concerns regarding this last study as there seem to be repeated measurements in some patients and inclusion of patients with ICP above the stated inclusion criteria. The reduction in CBV was believed to be caused mainly by a vasoconstriction induced by reduction in blood viscosity improving blood flow (Muizelaar et al., 1983). This cerebral vasoconstriction has, however, been shown not to occur in other studies (Ravussin et al., 1985; Auer and Haselsberger, 1987). Auer et al. gave mannitol during 15 minutes, which is more in line with clinical practice than the one minute used by Muizelaar et al., and Ravussin et al. found reduced ICP despite increased CBV.
It seems reasonable to speculate that instant, haemodynamic changes may account for some of the early (less than 15 minutes) effect seen on ICP after osmotherapy, whilst the osmotic effect is slower in onset, gradually dehydrating the brain towards a peak effect at 15 to 30 minutes after administration of a hypertonic solution (Ziai et al., 2007).

History
The first description of osmotherapy applied to the central nervous system (CNS), is attributed to Weed and McKibben in 1919 (Weed and McKibben, 1919a; Weed and McKibben, 1919b). As research fellows in the Army Neurosurgical Laboratory at the Johns Hopkins Medical School, they were attempting to measure the transport of sodium salts from the blood into the CSF in cats. Upon intravenous injection of small volumes of 30% hypertonic saline (HS), they measured a marked and sustained decrease in ICP (Weed and McKibben, 1919b). This they found was due to shrinkage of the brain. They went on to describe how they through a craniotomy defect could observe the brain shrink away after HS injection with maximum effect 15 to 30 minutes after completion of the injection (Weed and McKibben, 1919a).

In 1927, intravenous delivery of osmotic agents for clinical practice was first formalized by Fremont-Smith and Forbes (Fremont-Smith and Forbes, 1927). They first used concentrated urea. 11 years later they were followed by Hughes et al. who demonstrated that concentrated solutions of human plasma proteins could reduce raised ICP (Hughes et al., 1938). The use of plasma proteins was however limited because of fear of allergic reactions and high cost.

Wider attention was brought to the use of urea by Javid et al in the late 1950s (Javid and Settlage, 1956; Javid, 1961). With its low molecular weight of 60 Daltons, slow elimination from blood, and relatively slow BBB penetration ($\sigma = 0.48$) (Qureshi and Suarez,
2000), it was a potent osmotic agent. It had however a significant potential for rebound cerebral oedema and side effects like phlebitis and haemolysis.

During early 1960s two other compounds replaced urea; mannitol and glycerol. Glycerol, introduced in 1964 is a trivalent alchohol (1,2,3-propanetriol), partially metabolized to CO$_2$ and water (Cantore et al., 1964). With a reflection coefficient ($\sigma$) of 0.59 (Qureshi and Suarez, 2000), it has a significant potential for causing rebound cerebral oedema. Side effects include haemolysis, haemoglobinuria, renal failure, and hyperosmolar coma (Bhardwaj, 2007). Possibly due to tradition, glycerol has been used quite frequently throughout Asia and some centres in continental Europe, whereas mannitol has been the drug of choice in the UK and the Americas (Paczynski, 1997). Mannitol has also been the preferred choice in the Nordic countries. Only since late 80s has hypertonic saline, the compound that started it all, gained renewed interest.

**Mannitol**

As mentioned previously, mannitol has been the osmotic agent of choice in clinical practice in many countries for nearly five decades (Brain Trauma Foundation et al., 2007a). Mannitol has a molecular weight of 182 Daltons, and is an alcohol derivate of the sugar mannose. As opposed to urea, it has a short plasma half-life of 2 to 4 hours. The reflection coefficient ($\sigma$) is 0.9 (Qureshi and Suarez, 2000), which is much better than those of urea and glycerol. It does, however, leave the door open for rebound elevation of ICP upon repeated administrations. This has been much debated during the last two decades, and has reduced its use at least for repeated administrations (Garcia-Sola et al., 1991; Kaufmann and Cardoso, 1992; Kofke, 1993; Polderman et al., 2003). In a study by Rudehill et al. the level of mannitol in the CSF increased after a single intravenous administration, and did not start to fall during the first eight hours after administration (Rudehill et al., 1993). Other side effects are acute renal
failure, particularly if serum osmolarity is > 320 mOsm/L combined with hypovolaemia (Worthley et al., 1988; Bullock, 1995). Mannitol is also of course foremost a diuretic, and will upon repeated administration lead to hypovolaemia if volume is not adequately substituted.

**Hypertonic saline**

After Velasco et al. in 1980 showed how bled dogs could be haemodynamically resuscitated with 4 mL/kg of 7.0% saline (Velasco et al., 1980), HS was evaluated for rapid resuscitation of patients with haemorrhagic shock during the 1980s and 90s. A small study by De Felippe Jr et al. (de Felippe Jr et al., 1980) was followed by a series of large randomised studies conducted in the pre-hospital setting (Holcroft et al., 1987; Vassar et al., 1991; Mattox et al., 1991; Vassar et al., 1993a; Vassar et al., 1993b). In two of the studies by Vassar et al. (Vassar et al., 1991; Vassar et al., 1993a), improved survival was reported after HS as compared to isotonic resuscitation in patients suffering from traumatic brain injury (TBI); survival to discharge being 32 versus 16% in the first study and 34 versus 12% in the second. This boosted the wave of studies looking at HS and cerebral effects from the 1990s.

The reflection coefficient ($\sigma$) across the BBB for NaCl is 1.0 (Rapoport, 1976; Zornow, 1996; Qureshi and Suarez, 2000). In that respect, HS is an ideal osmotic agent. The main effect on elevated ICP is due to the “dehydrating” effect on the brain (Qureshi and Suarez, 2000; Ziai et al., 2007). The “dehydrating” effect of hypertonic saline (HS) has been shown both in animal studies (Todd et al., 1985; Zornow et al., 1989; Bacher et al., 1998; Toung et al., 2007; Chen et al., 2007) and in a MRI-study in humans (Saltarini et al., 2002). Theoretically most of the effect would be found in uninjured parts of the brain. This is supported by most studies (Zornow et al., 1989; Battistella and Wisner, 1991; Shackford et al., 1992). Normal brain tissue is “dehydrated” to accommodate the increase in intracranial
volume that results from oedema or haemorrhage. The effect in parts of the brain with injured BBB is more unpredictable (Chen et al., 2007).

Cerebrovascular endothelial cells and red blood cells are also dehydrated, improving CBF and oxygen delivery due to increased vessel diameter and reduced size of the blood cells (Mazzoni et al., 1990; Shackford et al., 1992; Doyle et al., 2001). And like mannitol, HS lowers blood viscosity which may induce vasoconstriction with reduced CBV (Burke et al., 1981; Muizelaar et al., 1983).

Another advantage of HS is that it does not have the potentially detrimental diuretic effect like mannitol, which may lead to hypovolaemia and impaired cerebral perfusion (Arai et al., 1986; Worthley et al., 1988).

There are a number of additional effects attributed to HS that deserve a brief mentioning even though most of the documentation is based on animal studies and has to date uncertain clinical implication. HS may have positive neurochemical effects, as HS solutions restore normal membrane resting potential by normalizing intracellular concentrations of sodium and chloride (Nakayama et al., 1985). HS may also have positive immunomodulatory effects on the inflammatory process generated by brain trauma, reducing leukocyte adherence and migration to injured parts of the brain (Hartl et al., 1997b). Several animal studies indicate a protective effect against bacterial infections (Coimbra et al., 1997; Shields et al., 2003; Chen et al., 2006), but very limited conclusions can be drawn as to the effect in humans (Kolsen-Petersen, 2004).

The saline concentration in the solutions that have been investigated ranges from 1.4 to 29.2%, and both solutions with and without the addition of a colloid have been used (Tables 1-2, page 21)(Table 3, page 23). The addition of a colloid, typically 6% dextrane or hydroxyethyl starch, has in haemodynamic resuscitation studies prolonged the haemodynamic effect compared with HS alone (Smith et al., 1985; Kramer et al., 1986; Velasco et al., 1989).
For the attenuating effect on raised ICP, the addition of a colloid has not altered the effect compared with HS alone (Vassar et al., 1993a). Other studies have shown that intravenous infusion of 6% dextrane or hydroxyethyl starch solutions without HS do not reduce ICP (Gunnar et al., 1986; Ducey et al., 1989). This fits well with what can be expected from theoretical considerations based on the different properties of the BBB and capillaries elsewhere in the body.

**Animal studies**

Todd et al. were among the first to re-examine the cerebral effects of hypertonic saline solutions (Todd et al., 1985). They demonstrated in rabbits a decrease in brain water content, a decrease in ICP, and an increase in cerebral blood flow (CBF) following infusion of hypertonic Ringers’s solution (osmolality of 480 mOsm/kg). A number of animal studies followed. Studies looking at the effect of HS on ICP, CBF, or cerebral oxygen delivery (CDO₂) are listed in Tables 1 and 2 (page 21).

Although there are indications of possible problems with rebound increase in ICP in the material from Prough et al. from 1999 (Prough et al., 1999), the overall picture is that of reliable reduction in ICP and improvement in CBF. The later findings by German groups of a possible neuroprotective effect of HS is also encouraging (Heimann et al., 2003; Zausinger et al., 2004; Bermueller et al., 2006). These findings are supported by other studies not looking at effect on ICP (Hamaguchi and Ogata, 1995; Hamaguchi et al., 2002; Thomale et al., 2004).
### Table 1. Animal studies investigating cerebral effects of HS without cerebral trauma.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Injury</th>
<th>Study solutions</th>
<th>Results after HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Todd et al., 1985</td>
<td>Rabbit</td>
<td>None</td>
<td>↓ ICP, ↑ CBF, cerebral dehydration</td>
</tr>
<tr>
<td>Prough et al., 1985</td>
<td>Dog</td>
<td>SS 7.5% S, RL</td>
<td>↓ ICP, ↔ CBF and CDO&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Gunnar et al., 1986</td>
<td>Dog</td>
<td>SS 3% S, 6% D</td>
<td>↑ ICP after HS, ↓ ICP after NS, D40</td>
</tr>
<tr>
<td>Prough et al., 1986</td>
<td>Dog</td>
<td>SS 7.5% S, RL</td>
<td>↓ ICP after HS, ↓ CBF and CDO&lt;sub&gt;2&lt;/sub&gt; both groups</td>
</tr>
<tr>
<td>Ducey et al., 1989</td>
<td>Pig</td>
<td>SS 6% S, 6% HE, NS, WB</td>
<td>↓ ICP, ↓ ICE</td>
</tr>
<tr>
<td>Schmoker et al., 1991</td>
<td>Pig</td>
<td>SS 1.5% SL, RL</td>
<td>↓ ICP, ↑ CBF, ↑ CDO&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

↓, decreased; ↑, increased; ↔, unchanged; SS, circulatory shock induced by bleeding; HS, hypertonic saline; S, saline; NS, 0.9% saline; RL, lactated Ringers; SL, sodium lactate; D, Dextran 40; HE, hetastarch; WB, whole blood; ICP, intracranial pressure; CBF, cerebral blood flow; CDO<sub>2</sub>, cerebral oxygen delivery; ICE, intracranial elastance.

### Table 2. Animal studies investigating cerebral effects of HS with cerebral trauma.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Injury</th>
<th>Study solutions</th>
<th>Results after HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gunnar et al., 1988</td>
<td>Dog</td>
<td>SS, EB 3% S, NS, 10% D</td>
<td>↓ ICP, ↓ BWC</td>
</tr>
<tr>
<td>Zornow et al., 1989</td>
<td>Rabbit</td>
<td>HD, Cryo 1.4% RL</td>
<td>Less ↑ ICP, ↓ contralat BWC</td>
</tr>
<tr>
<td>Battistella and Wisner, 1991</td>
<td>Sheep</td>
<td>HT, Cryo 7.5% S, RL</td>
<td>↓ ICP, ↓ contralat BWC</td>
</tr>
<tr>
<td>Walsh et al., 1991</td>
<td>Pig</td>
<td>SS, Cryo HSD, RL</td>
<td>↓ ICP, ↑ CBF</td>
</tr>
<tr>
<td>Prough et al., 1991</td>
<td>Dog</td>
<td>SS, SB 7.2% S, 0.8% S</td>
<td>↓ ICP, ↑ CBF</td>
</tr>
<tr>
<td>Shackford et al., 1992</td>
<td>Pig</td>
<td>Cryo 1.5% SL, RL</td>
<td>↓ ICP, ↑ CBF, ↑ CDO&lt;sub&gt;2&lt;/sub&gt;, ↑ contralat BWC</td>
</tr>
<tr>
<td>DeWitt et al., 1996</td>
<td>Cat</td>
<td>H, PFI 3% S, 10% HE</td>
<td>↓ CDO&lt;sub&gt;2&lt;/sub&gt; for both</td>
</tr>
<tr>
<td>Taylor et al., 1996</td>
<td>Piglet</td>
<td>SS, Cryo 7.5% S, RL</td>
<td>↓ ICP, ↑ ScO&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Anderson et al., 1997</td>
<td>Sheep</td>
<td>H, Cryo 7.5% S, RL</td>
<td>↓ ICP, BWC equal</td>
</tr>
<tr>
<td>Prough et al., 1999</td>
<td>Dog</td>
<td>SS, SB 7.2% S, 7.2% S/20% HES, 20% HES, 0.8% S</td>
<td>↓ ICP, rebound ↑ ICP</td>
</tr>
<tr>
<td>Heimann et al., 2003</td>
<td>Rat</td>
<td>VO 7.5% S/10% HES, 10% HES, NS</td>
<td>↑ CBF, ↓ infarct size</td>
</tr>
<tr>
<td>Zausinger et al., 2004</td>
<td>Rat</td>
<td>SAH HSD, 7.5% S, NS</td>
<td>↓ ICP, HSD also ↑ neurological recovery</td>
</tr>
<tr>
<td>Bermueller et al., 2006</td>
<td>Rat</td>
<td>SAH HSD, 7.2% S/ HES, M, NS</td>
<td>↓ ICP, HSD also ↓ morphological damage</td>
</tr>
</tbody>
</table>

↓, decreased; ↑, increased; ↔, unchanged; SS, circulatory shock induced by bleeding; HS, hypertonic saline; S, saline; NS, 0.9% saline; RL, lactated Ringers; SL, sodium lactate; D, Dextran 40; HSD, 7.5%S in 6%M HE; HES, hydroxyethyl starch; M, 20% mannitol; ICP, intracranial pressure; CBF, cerebral blood flow; CDO<sub>2</sub>, cerebral oxygen delivery; BWC, brain water content; ScO<sub>2</sub>, cerebrovascular oxygen saturation.
Human studies

Several human studies have been performed looking at the effect of HS on ICP (Table 3, page 23). Most of these were published prior to the publication of the studies included in this thesis, but also a handful during the time during completion of this thesis. I have included all of these in Table 3 (page 23) for completeness.

The main finding in these reports is that of a reliable reduction in ICP after HS administration. In studies comparing HS to mannitol, HS is either equal or superior to mannitol. The magnitude of the maximum effect is described, but information about the time course of the effect is most often lacking. When is maximum effect reached? How long does the effect last, and is there rebound in patients with damaged BBB?

Only two retrospective studies from Baltimore report negative effects. Increased in-hospital mortality was found in one study (Qureshi et al., 1999) and loss of effect on ICP after 3 – 4 days in another (Qureshi et al., 1998). Both these studies applied continuous infusion of 3% sodium chloride / sodium acetate during several days. The indication for HS was cerebral oedema with or without intracranial hypertension. Mean ICP before initiation of HS was < 20 mmHg in these studies and infusion was continued regardless of ICP. There was also a greater incidence of penetrating injury in the HS group in the study from 1999. My interpretation of these studies is that without signs of intracranial hypertension or decreased intracranial compliance, there is no clear indication for continuous infusion of HS.

Many of the studies are conducted with mixed patient populations, although there is a majority of TBI patients. All together there are only ten SAH patients included in the prospective studies. The effect of HS on ICP may very well differ between patient groups. Patients with localized BBB disruption will most probably respond much better to osmotherapy than those with generalized BBB disruption.
Table 3. Studies exploring the effect of hypertonic saline on ICP in humans.

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Study design</th>
<th>N</th>
<th>Study solutions</th>
<th>Results after HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worthley et al., 1988</td>
<td>Case-series</td>
<td>2</td>
<td>29.2% S (bolus)</td>
<td>Immediate ↓ ICP</td>
</tr>
<tr>
<td>Fisher et al., 1992</td>
<td>Prospective, randomized, cross-over</td>
<td>18</td>
<td>3% vs. 0.9% S (10mL/kg bolus)</td>
<td>↓ ICP</td>
</tr>
<tr>
<td>Einhaus et al., 1996</td>
<td>Case report</td>
<td>1</td>
<td>7.5% S (bolus)</td>
<td>Immediate ↓ ICP</td>
</tr>
<tr>
<td>Hart et al., 1997a</td>
<td>Prospective, observational</td>
<td>6 (32)</td>
<td>HSH (bolus)</td>
<td>↓ ICP, ↑ CPP, 5 survived</td>
</tr>
<tr>
<td>Shackford et al., 1998</td>
<td>Prospective, randomized</td>
<td>34</td>
<td>1.6% S vs. RL</td>
<td>Equally safe, HS group more severely ill</td>
</tr>
<tr>
<td>Qureshi et al., 1998</td>
<td>Prospective, randomized</td>
<td>27 (30)</td>
<td>3% S (cont. infusion)</td>
<td>↓ ICP, ↓ oedema, rebound after 3-4 days</td>
</tr>
<tr>
<td>Schwarz et al., 1998</td>
<td>Prospective, randomized, cross-over</td>
<td>9 (30)</td>
<td>100mL HSH, vs. 200mL, 20% M (bolus, 15 min.)</td>
<td>Mean ↓ ICP, HSH -11 mmHg, M -6 mmHg</td>
</tr>
<tr>
<td>Schatzmann et al., 1998</td>
<td>Prospective, observational</td>
<td>6 (42)</td>
<td>100mL 10% S (bolus, 5 min.)</td>
<td>↓ ICP, mean 43% from baseline, mean duration 101min.</td>
</tr>
<tr>
<td>Suarez et al., 1998</td>
<td>Prospective, randomized</td>
<td>32</td>
<td>1.7% S vs. RL (cont. infusion)</td>
<td>↓ ICP, ↓ ventilator time, ↓RDS, ↓survival</td>
</tr>
<tr>
<td>Suarez et al., 1999</td>
<td>Retrospective</td>
<td>29</td>
<td>3% S (cont. infusion)</td>
<td>Improved haemodynamics, no adverse effects</td>
</tr>
<tr>
<td>Horn et al., 1999</td>
<td>Prospective, randomized</td>
<td>10 (48)</td>
<td>2 mL/kg 7.5% S (bolus)</td>
<td>↓ ICP, mean 42% from baseline, mean duration 3 hours</td>
</tr>
<tr>
<td>Qureshi et al., 1999</td>
<td>Retrospective case-control</td>
<td>36 (46c)</td>
<td>3% S vs. NS (infusion)</td>
<td>↑ in-hospital mortality</td>
</tr>
<tr>
<td>Munar et al., 2000</td>
<td>Prospective, observational</td>
<td>14</td>
<td>1.5 mL/kg, 7.2% S (bolus, 15 min.)</td>
<td>↓ ICP, mean ~30% from baseline, ↑ CPP, ↑ CO</td>
</tr>
<tr>
<td>Khanna et al., 2000</td>
<td>Prospective, observational</td>
<td>10</td>
<td>3% S (cont. infusion)</td>
<td>↓ ICP, no adverse effects, peak serum sodium 157-187 mEq/L</td>
</tr>
<tr>
<td>Peterson et al., 2000</td>
<td>Retrospective</td>
<td>68</td>
<td>3% S (cont. infusion)</td>
<td>↓ ICP, no adverse effects, 3 dead due to ↑ ICP</td>
</tr>
<tr>
<td>De Vivo et al., 2001</td>
<td>Prospective, randomized</td>
<td>30</td>
<td>3% S vs. M (boluses, 3 days)</td>
<td>↓ ICP, ↔ CVP. M -1CVP</td>
</tr>
<tr>
<td>Viallet et al., 2003</td>
<td>Prospective, randomized</td>
<td>20</td>
<td>7.5% S vs. 20% M (2 mL/kg)</td>
<td>Less time with ↑ ICP, less clinical failure</td>
</tr>
<tr>
<td>Battison et al., 2005</td>
<td>Prospective, randomized, cross-over</td>
<td>9</td>
<td>100mL HSD vs. 200mL 20% M (bolus, 5 min.)</td>
<td>↓ ICP, greater reduction and longer duration</td>
</tr>
<tr>
<td>Harutjunyan et al., 2005</td>
<td>Prospective, randomized</td>
<td>32</td>
<td>HSH vs 15% M (1.4 vs 1.8 mL/kg)</td>
<td>↓ ICP, mean 57% vs 48% from baseline</td>
</tr>
<tr>
<td>Ware et al., 2005</td>
<td>Retrospective</td>
<td>13</td>
<td>23.4% S vs M (bolus, S after M)</td>
<td>↓ ICP, equal reduction, but longer duration</td>
</tr>
<tr>
<td>Huang et al., 2006</td>
<td>Prospective, observational</td>
<td>18 (38)</td>
<td>300 mL 3% S, (daily bolus, 50 min. if ↑ ICP)</td>
<td>↓ ICP, ↑ CPP, ↓PI</td>
</tr>
<tr>
<td>Koenig et al., 2008</td>
<td>Prospective, cohort</td>
<td>68 (76)</td>
<td>30-60 mL 23.4% S (bolus)</td>
<td>Reversal of TTH in 75% of cases, ↓ICP</td>
</tr>
</tbody>
</table>

↓, decreased; ↑, increased; ↔, unchanged; N, number of patients (interventions); ICP, intracranial pressure; CPP, cerebral perfusion pressure; PI, cerebrovascular pulsatility index; BO, brain oedema; TBI, traumatic brain injury; SAH, subarachnoid haemorrhage; PO, postoperative; BT, brain tumour; ICH, non-traumatic intracerebral haemorrhage; CI, cerebral infarction; TTH, transtentorial herniation; GCS, Glasgow coma score; CO, cardiac output; HS, hypertonic saline; S, saline; NS, 0.9% saline; HES, hydroxyethyl starch; RL, lactated Ringer; HSH, 7.2-7.5% HS in 6% HES; HSD, 7.5% S in 6%Dextran; M, mannitol; RDS, respiratory distress syndrome
Intracranial pressure monitoring

Mean ICP

Current state-of-art technology computes mean ICP during short time windows (e.g. 5 – 15 s duration). ICP can be measured by a number of different techniques, unfortunately all invasive. This means that measuring ICP must be weighed against the risks of infection and haemorrhage (Ghajar, 1995). The measurement of ICP via an intraventricular catheter, is internationally considered “the gold standard” (Guillaume and Janny, 1951; Lundberg, 1960; Czosnyka and Pickard, 2004; Steiner and Andrews, 2006). The advantages of this technique are the possibility of CSF drainage and the possibility to perform re-zeroing of the system, i.e. re-calibration towards atmospheric pressure. This technique requires, however, meticulous attention to adjustments of the zero level as the patient’s position is changed, and the monitoring is of course lost if the drain is clotted. The alternative technique is the use of a miniature, solid, intraparenchymal sensor. These allow continuous pressure monitoring at the same time as CSF can be drained through a ventricular catheter. The main disadvantage of most of the available systems is that they can not be re-calibrated once inserted, and that the zero pressure level may drift (Morgalla et al., 2001; Piper et al., 2001). Other techniques like subarachnoid or epidural probes, lumbar CSF pressure, tympanic membrane displacement, or transcranial Doppler, have not shown sufficient reliability for clinical use (Steiner and Andrews, 2006).

There are other problems with the measurement of mean ICP in addition to the technical aspects. We see in clinical practice how mean ICP changes abruptly when the patient’s position is changed. If an intraparenchymal probe is inserted on the right side, and the patients head is turned from resting on the left side to the right side, measured mean ICP might increase as much as 10 mmHg. Looking at trend plots of mean ICP, we regularly see
these different ICP levels directly relating to patient position. This can be explained by the simple fact that mean ICP is influenced by the weight of the brain above the point of measurement. Eide demonstrated in a small study how mean ICP measurements recorded simultaneously from two different intraparynchamal sensors differed considerably (Eide, 2006b). A difference of above 5 mmHg was recorded 13% of the time and above 10 mmHg 6% of the time. He describes how one sensor showed mean ICP > 20 mmHg while the other showed < 15 mmHg. Such a difference might have direct implications on patient treatment, no matter what the cause of the difference is.

Another problem is deciding on what level of mean ICP should bring about an intervention to decrease ICP. What is a normal ICP? In young healthy volunteers lying down, average mean ICP was 11 mmHg (range 7 to 15 mmHg) (Albeck et al., 1991). In the upright position mean ICP was found to be in the range of -5 to +5 mmHg (Chapman et al., 1990). Starting measurements from the supine position, the decrease to this level was found to occur when elevating the head to about 45°, not changing much thereafter. In evaluating different mean ICP levels to outcome, one should therefore pay close attention to the degree of head elevation in order to be able to compare results.

Although there is no definite agreement on the threshold for treatment, the guidelines from the Brain Trauma Foundation recommend treatment of mean ICP > 20 – 25 mmHg in traumatic brain injury (TBI) patients (Brain Trauma Foundation et al., 2007b). The decision in an individual patient is of course taken looking at ICP together with other variables like CPP, transcranial Doppler, clinical status, and radiological findings. It is not within the scope of this thesis to go into all these considerations, but at this point only to emphasise the need for further research that can improve the predictive power of our intracranial pressure measurements.
ICP waveform analysis

One path that might prove worthwhile is looking at the intracranial pressure wave and intracranial compliance. Intracranial compliance relates to the changes in ICP subsequent to changes in intracranial volume at different pressure levels. When ICP is low and compliance is high, a small increase in volume only causes a small increase in pressure. If, however, the pressure is high and the compliance is low, this same increase in volume yields a far greater increase in pressure. It has been shown that this intracranial pressure-volume relationship is better described by a pulsatile than a static ICP (Avezaat et al., 1979; Gonzalez-Darder and Barcia-Salorio, 1989).

A method for direct monitoring of brain compliance has been implemented in the Spiegelberg Brain Compliance monitor. This method relies on the evaluation of the pressure response to known small volume additions by inflating and deflating a balloon inserted within the cerebrospinal space. Initial trials indicate its usefulness, but implication for outcome remains to be demonstrated (Piper et al., 1999; Yau et al., 2002).

A lot of work has been done by a group in Cambridge, UK, looking at waveform analysis of ICP (pulsatile ICP) (Czosnyka and Pickard, 2004). The ICP waveform consists of several components, but it is especially the amplitude of the component with a frequency equal to the heart rate that has gained most focus, the intracranial pulse pressure or ICP amplitude. The Cambridge group has described two ICP derived indexes (Czosnyka and Pickard, 2004). The first is called RAP (correlation coefficient (R) between AMP amplitude (A) and mean pressure (P); index of compensatory reserve). When RAP is close to +1, the amplitude varies directly with ICP, indicating a low intracranial compensatory reserve. The second index is a pressure-reactivity index called PRx. A positive index is correlated with poor autoregulation. Abnormal values have been demonstrated to predict poor outcome after head injury (Steiner et al., 2002).
The magnitude of “slow ICP waves” (frequency ½ - 3 per minute) has also been shown to correlate with outcome, a greater magnitude indicating favourable outcome (Lundberg, 1960; Balestreri et al., 2004).

My curiosity about waveform analysis and its possible use in clinical practice was awakened by the work performed at our institution by Eide and co-workers. He has developed a method of actually continuously measuring the heartbeat to heartbeat intracranial pulse pressure and displaying this in real time at the bed side (Eide, 2006a). Previously, information about single ICP waves has been derived from spectral analysis using fast Fourier transformation (FFT) (Christensen and Borgesen, 1989). FFT does, however, not include an algorithm for identification of the single ICP waves. The intracranial pulse pressure recorded using the new method is called “mean ICP wave amplitude”, and it was found to relate significantly to both the acute clinical state (Glasgow Coma Score, GCS) and the final clinical outcome (Glasgow Outcome Score, GOS) in SAH patients. This relationship could in that study not be demonstrated for mean ICP and mean CPP (Eide and Sorteberg, 2006).

Moreover, a case report showed how a long-standing bad clinical state of a SAH patient was rapidly changed by turning management from being guided by static ICP (mean ICP) to being pulsatility (or waveform) guided according to the mean ICP wave amplitude (Eide et al., 2007c). It was also reported how a reduction in intracranial pulsatility could be achieved by increased drainage of cerebro-spinal fluid (CSF) via an external ventricular drain (EVD) (Eide et al., 2007c). Given the positive indications that mean ICP wave amplitude could predict outcome, I found it important to investigate whether a medical intervention with HS could decrease mean ICP wave amplitude. An additional incentive for contributing research results regarding this new variable is all the technical and practical difficulties related to mean ICP that I have mentioned earlier.
AIMS OF THE THESIS

1. Describe the effects of bolus infusion of 7.2% (72 mg/mL) saline in 6% (60 mg/mL) hydroxyethyl starch 200/0.5 solution (HSS) on the intracranial pressure (ICP) variables, mean ICP and mean ICP wave amplitude, and cerebral perfusion pressure (CPP) in patients with subarachnoid haemorrhage (SAH).
2. Describe the time course of these effects, including time to maximum effect.
3. Describe the magnitude of these effects.
4. Describe the changes in serum sodium concentration, and how serum sodium is related to ICP during the study period.
5. Describe haemodynamic effects.
6. Describe how mean ICP and mean ICP wave amplitude are related.
7. Compare the effect of HSS on mean ICP with the effect on mean ICP wave amplitude (intracranial pulse pressure).
8. Compare the effect on intracranial pulse pressure with the effect on systemic arterial pulse pressure.
METHODS

All data in the three studies have been collected from patients suffering from acute, non-traumatic subarachnoid haemorrhage (SAH) admitted to the Intensive Care Unit at Rikshospitalet University Hospital. All patients included were unconscious due to the nature of their disease and could not give their informed consent to participation. Possible risks and benefits were therefore given thorough evaluation. The protocols were approved by the Regional Ethics Committee for Medical Research and the Norwegian Medicines Agency. Close relatives were given oral and written information in accordance with the terms for approval by the Ethics Committee.

Study design

A common denominator of the studies was the effort taken to ensure as laboratory-like conditions as possible, given a clinical setting. The first measure to achieve this was of course to only include SAH patients, the second measure was to only include patients which were relatively stable before intervention, and the third was to make sure that nothing was done with the patient during the study period unless dictated by the rescue treatment protocol.

In both Study I and II we looked at effects of HSS on mean ICP, CPP, and haemodynamics during a 210 minutes study period. In Study I relevant patients with mean ICP > 20 mmHg were included. This being an observational study, Study II was given a randomised, single-blinded, placebo-controlled design including patients with mean ICP < 20 mmHg. Judged together, these two studies would then give sound evidence of an effect (Study II), magnitude of effect (Study I), and time course of the effect (Study I and II). Study III utilized data collected in a still ongoing prospective study looking at different ICP variables and their association to outcome. Instances where known doses of HSS were administered at
known times were selected from a large database of pressure recordings, and before and after values were analysed.

All data were recorded prospectively. In Study I and II they were analysed according to the predetermined plan drawn up in the protocols. In Study III, the data were prospectively collected as part of a different study still ongoing. The protocol for Study III was designed after data collection had started.

Data collection

Intracranial pressure was measured via a solid ICP sensor (Codman MicroSensor™, Codman, Raynham, MA) coupled to a Codman® pressure transducer (Codman ICP Express™, Codman, Raynham, MA). For the continuous arterial blood pressure (ABP) monitoring, an arterial cannula was placed in a radial or femoral artery and connected to a Baxter fluid sensor (Baxter, Deerfield, IL). Arterial blood pressure was zeroed at the level of the heart. Both signals together with heart rate (HR), central venous pressure (CVP), and peripheral oxygen saturation (SpO₂) were coupled to a vital signs Siemens 9000XL Series Monitor (Siemens AG, Munich, Germany). Cardiac index (CI), intrathoracic blood volume index (ITBI), and extravascular lung water index (ELWI) were measured by use of the PiCCO system (Pulsion Medical Systems, Munich, Germany). Arterial blood gases, pH, haemoglobin, and sodium were analysed with the ABL 725 (Radiometer, Denmark).

In study I and II, values from the Siemens monitor and the PiCCO system were registered electronically on a bed side computer every 30 seconds (LabView, National Instruments, Austin, TX). False blood pressure values due to blood sampling were removed manually before analysis.

In Study III a different setup for electronic data harvest was used. By means of the Siemens Infinity Gateway Software, the continuous ICP and ABP signals were transferred on
line via the hospital network to a computer server and stored as raw data files with sampling rates of 100 Hz. These data were analysed retrospectively using an algorithm implemented in the software SM NeuroWave Version 2.0 (Eide, 2006a). Information on the time and amount of hypertonic saline administered was collected from the patient charts.

**Statistical methods**

All patients included in the studies were reported according to the principle of intention-to-treat. Study I and II are very similar in design. Repeated measurements of continuous data were collected from different individuals. While Study I was an observational study of ten interventions in seven patients, Study II was a placebo-controlled comparison of two groups, total 22 patients. Mean values of measured variables for each patient from a 5 min period just prior to infusion of study drug served as baseline. For data acquired electronically every 30 seconds, the mean value of all 5 minute periods throughout the 210 minute study period were calculated and used for analysis.

In Study I comparisons of values at the time of maximum effect and at the end of the study were compared with baseline values applying Wilcoxon’s test for paired samples. Even though the changes were highly significant, we chose to display the graphs of mean ICP and CPP for the ten individual cases. Since the number of cases was so low, we found this to be the best way to convey the results truthfully to the reader.

In Study II baseline values were also calculated as the mean of a 5-minute period prior to infusion of HSS, and mean values for each 5-minute interval throughout the study period were used for analysis like in Study I. Differences between the groups were assessed by un-paired Student’s *t*-test with Welch correction when there were unequal variance. For analysis of demographic data, Mann-Whitney and chi-square tests were also used. The number of patients was equal to the number of cases. In this study we did not only compare maximum
effect to baseline levels, we calculated the area under the curve for the different variables and standardized by the length of the study to get the mean change for the whole period. This is a recommended approach to statistical analysis of serial measurements (Matthews et al., 1990).

In Study III we had a total of 52 registrations from 20 patients, ranging from one to six per patient. Due to possible bias because of repeated measurements, only the first registration in each patient was included in the main results. This is in accordance with the statistical recommendations that the sampling unit, or the “unit of analysis”, must be the patient in studies like this one (Altman and Bland, 1997). We did however include information also about calculations based on the total material of 52 registrations. A paired t-test was applied comparing values before and after intervention for each variable, correlation was calculated according to Pearson, and standard linear and multiple regression analyses were applied. P-values <0.05/number of comparisons (Bonferroni correction) were considered significant.
SYNOPSIS OF RESULTS

Paper I

This study was designed to document the short term effects of 7.2% (72 mg/mL) saline in 6% (60 mg/mL) hydroxyethyl starch 200/0.5 solution (HyperHAES®) (HSS) on intracranial hypertension after subarachnoid haemorrhage (SAH). Primary outcome variables were changes in mean intracranial pressure (ICP), changes in cerebral perfusion pressure (CPP), and number of treatment failures, here defined as not reaching mean ICP < 20 mmHg and CPP > 60 mmHg during the study period. Secondary outcome variables were changes in cardiac index (CI), intrathoracic blood volume index (ITBI), and extravascular lung water index (ELWI).

Ten interventions in seven patients were included. All patients suffered from spontaneous SAH, their source of bleeding had been secured, and they had raised mean ICP > 20 mmHg. A bolus of 2 mL/kg of HSS was infused during 20 minutes, and registrations continued for a total of 210 minutes. A laboratory like setting was pursued.

All interventions resulted in decreased mean ICP < 20 mmHg and elevation of CPP > 60 mmHg, i.e. zero treatment failures. The mean value for maximum mean ICP decrease in percent of baseline was 58%, a mean decrease of 14.3 mmHg from a baseline of 25 mmHg. Maximum effect was reached at 40 minutes after start of infusion. The mean peak increase in CPP was 26%. In the eight cases recorded for 210 minutes, the mean ICP was still 35% below baseline values at the end of the study. The time course of changes in ICP and CPP is displayed in Figure 1B (page 38). We could also demonstrate an inverse relationship between mean ICP and serum sodium levels. The maximum mean serum sodium increase was 6.6 mmol/L. There were no statistically significant changes to the secondary outcome variables (measured in only five cases), only a trend towards increase in CI ($p = 0.06$) and ITBI ($p = 0.06$).
We concluded that the infusion of 2 mL/kg of HSS had a predictable and clinically significant beneficial effect on mean ICP and CPP.

**Paper II**

Study I being an observational study, this study was designed to strengthen those results. A group given 2 mL/kg of HSS was compared with a placebo group receiving 2 mL/kg of normal saline (NS). In order to do that, the inclusion criterion as to intracranial pressure was mean ICP between 10 and 20 mmHg. The design apart from this was very similar to Study I with almost the same outcome variables. Changes in mean ICP and CPP were however primarily analysed as the changes in mean values for the entire study period, not only maximum change and change at the end of the study period.

In the placebo-group, there were no changes in any variables indicating that the study design was valid. In the HSS group we found a significant reduction in mean ICP and increase in CPP. Mean difference between the groups (HSS – NS) in average ΔICP was -3.0 mmHg and ΔCPP was 5.4 mmHg. Mean maximal change in mean ICP was -5.6 mmHg in the HSS group. No rebound increase in ICP was found during the study period. The temporal change was very similar to the one found in Study I (Figure 2, page 42). In addition, we demonstrated a significant increase in cardiac output in the HSS group. The changes in serum sodium found in the HSS group was quite similar to the findings in Study I, mean maximum increase of 5.6 mmol/L measured at 30 minutes, and a level 3.3 mmol/L above baseline at the end of the study.

We concluded that HSS reduce mean ICP and increase CPP in SAH patients, and that positive haemodynamic effects can be found. Judged together with Study I we concluded that HSS attenuates increased mean ICP in SAH patients with a maximum effect reached at 20-30
minutes after the completion of the infusion. The magnitude of the effect would be expected to be in the range demonstrated in Study I.

**Paper III**

In this study we compared the effect of HSS on mean ICP with the effect on mean ICP wave amplitude in SAH patients. Mean ICP wave amplitude is the intracranial pulse pressure recorded according to the algorithm developed by Eide; each cardiac beat-induced single pressure wave is automatically identified, and the pressure variables are calculated for consecutive 6-second time windows (Eide, 2006a). We also compared the effect on mean ICP wave amplitude with the effect on systemic arterial pulse pressure.

The study included 52 interventions with different amounts of HSS in 20 SAH patients. Only the first intervention in each patient was included in the main results due to statistical reasons. It was found that both mean ICP and mean ICP wave amplitude were attenuated by HSS. A correlation was found between change in mean ICP and mean ICP wave amplitude, but no correlation was found between baseline values of mean ICP and mean ICP wave amplitude. There was also a difference as to whether the treatment goal was reached. The goals were defined as mean ICP < 15 mmHg and mean ICP wave amplitude < 5 mmHg. The goal was reached in 65% of cases for mean ICP, while only in 30% of cases for mean ICP wave amplitude. The study also documented that there was no correlation between systemic arterial pulse pressure and intracranial pulse pressure, indicating that the intracranial pulse pressure is no reflection of systemic pressure changes but represents the response to the intracranial volume changes with each heartbeat.

In conclusion, the study documents for the first time that a drug, in this case HSS, has an attenuating effect on pulsatile ICP. The low percentage of target achievement for mean ICP wave amplitude indicates, however, that the intracranial compliance state was less favourable.
than expected in a majority of these SAH patients with mean ICP and mean CPP values within normal ranges. The results also showed that the value of mean ICP wave amplitude could not be deduced from the value of mean ICP or vice versa in any given individual patient.
DISCUSSION

All three studies included in this thesis are about the effect of 7.2% (72 mg/mL) saline in 6% (60 mg/mL) hydroxyethyl starch 200/0.5 solution (HSS) on intracranial pressure (ICP) in patients suffering from acute, spontaneous, subarachnoid haemorrhage (SAH). There are, however, thematically two different trails that are relevant to separate. Study I and II on one hand, are documenting effects on the well known and much investigated variables mean ICP and cerebral perfusion pressure (CPP). Study III on the other hand, is more on the edge to less well described territory, contributing a piece of evidence concerning the newly described intracranial pressure variable; mean ICP wave amplitude.

To put the perspective right, the findings in this thesis can tell nothing about whether the use of HSS had any bearing on neurological outcome in the patients studied. But being based on clinical studies, the results can, judged together with available literature, have direct implications for our current practice treating these patients. I hope to supply the fundament for an educated answer to whether clinical practice can be modified based on the findings in this thesis.

Before continuing, I would like to make a small pause, and close a 85 years long loop between the initial findings in 1919 by Capt. Lewis H. Weed and 1st Lt. Paul S. McKibben at The Army Neuro-Surgical Laboratory, Johns Hopkins Medical School, their extensive research in cats, and our own findings in patients admitted to our intensive care unit at the beginning of the following century. The point is to visually illustrate the similarities between an ICP curve from one of their publications (Weed and McKibben, 1919b) (Figure 1A, page 38) with our ICP curve from Study I (Figure 1B, page 38).

During the time I have worked with this thesis, it has remained a mystery to me why hypertonic saline was not re-discovered before, as an osmotic agent in the context of
intracranial hypertension. HS is cheap and has a much higher blood brain barrier (BBB) reflection coefficient than the other drugs studied throughout the 20th century.

Figure 1. A: ICP curve from cat no. 1271 after IV infusion of 12 mL of 30% saline (Weed and McKibben, 1919b). B: Mean change in ICP and CPP after IV infusion of 2 mL/kg of 7.2% saline in 6% hydroxyethyl starch 200/0.5 solution in SAH patients, n = 10 (Paper I). ICP, intracranial pressure; CPP, cerebral perfusion pressure; IV, intravenous. Figure 1A used with the permission from The American Physiological Society.

The relevance of ICP and CPP

A fundamental assumption for the use of osmotherapy to reduce ICP is that raised ICP correlates with bad outcome. Even though there is no single study that beyond doubt proves that monitoring of ICP improves outcome as opposed to not monitoring ICP, there are strong indications that support its value.

With data from 428 traumatic brain injury (TBI) patients, Marmarou et al. found that the proportion of hourly ICP readings greater than 20 mmHg was highly significant in explaining outcome (Marmarou et al., 1991). Several other authors have also demonstrated worsened outcome in patients with increased ICP (Marshall et al., 1979; Narayan et al., 1981; Fearnside et al., 1993). However, Resnick et al. failed to demonstrate such a correlation for ICP > 20 mmHg measured more than 96 hours after injury (Resnick et al., 1997). In 1999, Robertson et al. published a randomised study in 189 patients with severe head injury,
demonstrating that secondary ischaemic insults could be prevented with the implementation of a target management protocol based on ICP and CPP (Robertson et al., 1999). Patel and co-workers have published an abstract showing a mortality rate twice as high among patients treated in non-neurosurgical units compared with patients treated in neurosurgical units (Patel et al., 2003). The availability of ICP monitoring is of course only one out of many factors differing between the groups in this study. All of these studies refer to TBI patients, and Treggiari et al. have summarised evidence in a recent review (Treggiari et al., 2007).

Citerio et al. have published a survey looking at the treatment of 350 SAH patients in Italian neurosurgical centres, and found high intracranial pressure to be an independent factor related to unfavourable outcome (Citerio et al., 2007). Two groups have found outcome to be related to mean ICP and pulsatility in SAH patients (Eide and Sorteberg, 2006; Soehle et al., 2007). Finally, Zanier et al. have documented the clinical advantages of monitoring ICP via a computerised system over manual recordings (Zanier et al., 2007). Based on all this I find it safe to conclude that monitoring of ICP and CPP is valuable to the patients suffering from severe head injury and severe SAH.

**Different ICP variables**

As pointed out earlier, the first two papers are concerned with mean ICP, and the last also with mean ICP wave amplitude. We have in the last paper referred to the two ICP variables respectively as static and pulsatile ICP. The pulsatile ICP reflects the difference between systolic and diastolic ICP, the static ICP (mean ICP) however, does not carry any information about the shape of the ICP curve. The static ICP is influenced by a number of factors besides pathological processes within the skull. Methodological factors such as the point of measurement and baseline pressure level determined by zero calibration and drift, greatly impacts the final measurement and has been discussed previously.
Pulsatile ICP (mean ICP wave amplitude) or intracranial pulse pressure is however in many respects a more robust variable. It describes the dynamic pressure response evoked by each cardiac beat. It does not need a correct zero calibration and is not influenced by drift of the zero level (Eide, 2006b). Further, it is not influenced by alterations in head position like described for mean ICP. In the study by Eide, while mean ICP differed considerably between two sensors, the differences in single pressure wave amplitude were marginal (Eide, 2006b). A difference of > 1 mmHg was found in only 0.8% of the time windows registered. Also, the intracranial compliance is better described by the pulsatile than the static ICP (Avezaat et al., 1979; Gonzalez-Darder and Barcia-Salorio, 1989; Eide et al., 2007a). With the availability of pulsatile ICP at the bed-side in real time, I find this variable worth investigating as a supplement to current standard neuromonitoring.

Effects of HSS on mean ICP and CPP in SAH patients

In Table 3 (page 23) I have listed the clinical studies looking at different concentrations of HS used with the intention of controlling raised ICP. There are few SAH patients included in these studies, and there are no studies with only SAH patients. There is also little information about the time course of the effect. Inspired by this lack of knowledge, the two first studies were designed to determine the short time effects on mean ICP and CPP of a HSS infusion in SAH patients only. The reason that there is two and not one study is that I wanted to carry out this research in a fashion as controlled as possible given a clinical setting, including a placebo control. A placebo control group could not be justified including patients with mean ICP > 20 mmHg, which is the group of patients that is relevant to look at. Two quite similar studies were therefore designed, one observational where all patients had mean ICP > 20 mmHg, and one placebo-controlled where the patients had mean ICP 10 – 20 mmHg. An observational study can never prove that an intervention was the cause of changes documented. The changes
could be due to natural courses or the effect of other interventions even if everything is kept unaltered. The thought was that if the findings were similar in the two studies, the placebo-controlled study would strengthen the findings from the observational study. The magnitude of the effect of HSS would be reflected in the observational study where the inclusion criteria for osmotherapy were relevant. In both studies we paid much attention to keeping all other things that might affect ICP constant during the study period. No sudden increase in ICP should lead to inclusion and a five minute period prior to infusion of HSS supplied baseline values. During the 210 minute study period, the patients were not stimulated, their position were unchanged, likewise ventilation, infusion rates for vasopressors, sedatives, and fluids. The level of resistance towards CSF drainage was kept unaltered.

The results in the group that received HSS in Study II did closely mimic those of Study I with a fall in mean ICP and rise in CPP, though with less absolute change as expected, as the patients included in Study II had far lower ICP at inclusion. There was no change in the placebo group (Figure 2, page 42). This indicated that the study design was valid, and that we managed to control other variables that might have affected ICP. We therefore concluded that HSS attenuates mean ICP and increases CPP in SAH patients.

**Temporal pattern of change**

The curves in Figure 2 (page 42) and Figure 1B (page 38) illustrates another important aspect; i.e. the temporal pattern of the effect. Maximum effect is not reached immediately, as it is when arterial CO₂ partial pressure is reduced by hyperventilation. In our studies it took about twice the infusion time before the maximum effect was reached. In Weed and McKibben’s study it took 25-30 minutes after the end of the bolus (given during five minutes) (Figure 1A, page 38). I have found only two clinical studies that contain such information. The first is a report of two TBI patients given 250 and 100 mmol of NaCl during 10 minutes respectively.
Figure 2. Changes in intracranial pressure (ICP) (top panel), and cerebral perfusion pressure (CPP) (bottom panel), after infusion of 2 mL/kg of study solution. HSS, 7.2% saline in 6% hydroxyethyl starch; NS, normal saline.
Maximum effect was reached about 20 minutes after the end of the infusions deduced from graphs included in the paper. The second report is in a study by Battison et al. including six TBI and three SAH patients, where HS was infused during 5 minutes. The paper includes a time-series plot from one patient, where the time to maximum effect seems to be 20 – 30 minutes (Battison et al., 2005). In our studies I and II, average time to maximum effect from start of infusion was 40 and 60 minutes respectively, the infusion times being 20 and 30 minutes.

This is important information both for the practitioner and the scientist. For the scientist, this indicates that the major effect of HS in the brain is due to removal of water, not mainly due to haemodynamic effects that would be expected to display an immediate effect. It may also say something about the properties of Aquaporine-4, if it is correct that these channels represent a rate-limiting step for water flux across the blood-brain-barrier (BBB).

For the practitioner using HS in clinical practice, it is very important to know when maximum effect of the intervention can be expected.

**Study solution**

Our choice of HS solution should be commented on. We chose a commercially available solution (HyperHAES®) containing 7.2% (72 mg/mL) saline in 6% (60 mg/mL) hydroxyethyl starch 200/0.5 (HSS). Converted to mmol, the sodium content is 1.23 mmol/mL. This solution was chosen for several reasons. The combination of 7.2 to 7.5% saline in either hydroxyethyl starch or dextrane has been extensively used in clinical research (Holcroft et al., 1987; Vassar et al., 1991; Mattox et al., 1991; Vassar et al., 1993a; Vassar et al., 1993b), and is as such known to be safe. We wanted our findings to be readily transferable to clinical practice, and using a solution that is available seemed sensible. 3% saline is quite frequently used in publications from the United States, but is seldom in stock in Norwegian hospitals. For the
reasons mentioned, and for issues related to the use of new drugs in medical research, we did not want to prepare our own solution for these studies. All our patients were sedated and had a central venous catheter in place, so the hypertonicity was not a problem. In acute, pre-hospital settings, the solution can also be given in a peripheral vein. Using a less concentrated solution would also have yielded a higher volume load which could become a problem in some patients with cardiac and/or renal impairments.

As mentioned previously under Introduction (page 19), the addition of 6% hydroxyethyl starch or dextrane to HS has been shown to prolong a positive haemodynamic effect, but not influence the effect on ICP. I therefore find it justified to attribute the intracranial pressure effects documented in our three studies to the HS component of the HSS solution.

Dose and practical use

The dose used in the first two studies was 2 mL/kg of 7.2% saline in 6% hydroxyethyl starch (HSS) (2.46 mmol Na⁺/kg). This is half of the conventional dose used in small-volume haemodynamic resuscitation research, but we had found 2 mL/kg to be sufficient in pilots prior to the studies. The idea was to not use a higher dose than necessary and thereby not increase serum sodium more than necessary, so that the treatment could be repeated if the clinical state indicates that. As discussed in Paper II, the findings from these studies indicate that a standard dose might be lowered from 2 mL/kg, as the maximum reduction in mean ICP in Paper I was > 50%. We now recommend a dose of 1 – 2 mL/kg. In practical use this has evolved into a standard dose of 100 mL of HSS during 10-15 minutes in the average 60 – 90 kg adult. However, a proper dose-finding study should be made.

Are bolus doses the optimal way of administering HS as osmotherapy? There is no definite answer to that. Most of the clinical studies listed in Table 3 (page 23) report only
single or repeated boluses, but some have used continuous infusion. Simma et al. randomised children with TBI to an infusion of lactated Ringer’s solution (sodium 131 mmol/L) or HS (sodium 268 mmol/L) with the goal of a serum sodium of 145-150 mmol/L during three days in the HS group. An increase in serum sodium correlated with lower ICP and higher CPP. They also reported fewer interventions, fewer complications, and shorter ICU stay in the HS group (Simma et al., 1998). Qureshi et al. on the other hand reported increased in-hospital mortality in a group of TBI-patients receiving a 3% HS-infusion as compared to normal saline in a retrospective study (Qureshi et al., 1999). The infusion was targeted at a serum sodium level of 145 – 155 mmol/L. There was, however, more penetrating injury in the HS group and the infusion was continued even when mean ICP was normal. There are two studies on children with TBI from San Diego applying a different approach (Khanna et al., 2000; Peterson et al., 2000). In these studies, HS is infused on a sliding scale to achieve a target serum sodium level that would maintain mean ICP < 20 mmHg. The results in these studies were promising with good effect on ICP and CPP, and they also reported very high serum sodium levels without adverse effects, mean highest level in the study by Khanna et al. was 170.7 mEq/L (range, 157 – 187 mEq/L).

I find the sliding scale approach logic, that the dose of HS should be dictated by the need, here defined by the level of mean ICP, instead of targeting a predefined level for serum sodium. It also underlines the need to pay attention to the serum sodium level at all times, not allowing it to drift. However, in clinical practice there is often a need for a bolus intervention in order to treat an increased ICP. Mere adjustments of a continuous infusion would not take effect rapidly enough. I would therefore recommend to give a bolus of HS as described previously when ICP > 20 mmHg and osmotherapy is indicated, followed by a continuous infusion to maintain the serum sodium level achieved after the bolus. When needed, a new
bolus can be administered, and the infusion continued to maintain the new sodium level. This can be pictured as a “stair-case approach” with respect to the serum sodium level.

**Adverse effects**

The classic adverse effect described in patients with rapidly increased serum sodium is central pontine myelinolysis (CPM). This has typically been described after rapid correction of pre-existing chronic hyponatraemia (Sterns et al., 1986; Vassar et al., 1990; Qureshi and Suarez, 2000; Verbalis, 2006). CPM has never been reported after elevation of a normal serum sodium level (Qureshi and Suarez, 2000; Himmelseher, 2007), but breakdown of the BBB followed by myelinolysis can occur if serum osmolality reaches 370 – 380 mOsm/kg (Soupart et al., 1996). Intracranial haemorrhages have been reported in small children and cats after abrupt changes in serum sodium (Finberg, 1967), but does not seem to be an issue in the context of adult neurointensive care. However, we have in our institution implemented safety precautions implying that one should avoid increasing serum sodium more than 15 mmol/L/day. We found in Study I and II mean maximum increase in serum sodium well within this limit; 6.6 and 5.6 mmol/L after 2 mL/kg of HSS.

Even though the reflection coefficient (σ) across intact BBB for NaCl is 1.0, one has to be aware of possible rebound increase in ICP. Since one can imagine all degrees of damage to the BBB, NaCl might leek into brain tissue in injured areas, later contributing to rebound increase in ICP. One has also to be aware of the transport of organic osmolytes, e.g. myoinositol, glutamine, glutamate, taurine, and urea into the brain, gradually compensating for the acute hyperosmolar state created intravascularly after HS. (Lien et al., 1990; Sterns and Silver, 2006; Verbalis, 2006). This means, that after culmination of the intracerebral hypertension, one has to carefully and in a controlled manner reduce the serum sodium level back toward normal levels, allowing the brain to lose the accumulated organic osmolytes.
again. Fortunately, the loss of osmolytes is more rapid than the uptake (Verbalis, 2006), but we recommend a reduction of serum sodium of no more than 10 mmol/L/day. I think that caution in tapering of the hypernatremic state can eliminate some problems that can be misconceived as rebound phenomena.

We do also advise caution in patients with unsecured aneurysms. A substantial intracranial volume and pressure reduction might precipitate re-bleeding. I have however never seen figures relating re-bleeding to the application of osmotherapy, but the general risk of very early re-bleeding (first 24 hours) is as high as 15% when no antifibrinolytic drugs are given (Hillman et al., 2002).

When using HS one has also always to be aware of the acute volume load that is introduced to the circulation, paying special attention to patients with pre-existing heart failure. We have, however, not encountered problems with this using 1 – 2 mL/kg of HSS. Neither have we been able to attribute special clinical problems to the inevitable hyperchloremic acidosis induced by the continuous and/or repeated administration of NaCl.

A significant risk of acute renal failure exists when mannitol is administered in large doses, especially when serum osmolarity is > 320 mmol/L (Bullock, 1995) and the patient is hypovolemic. This does not seem to be a problem to the same extent with HS, and a serum osmolality > 320 mmol/L is not considered a contraindication to its use (Qureshi and Suarez, 2000). And as opposed to mannitol, repeated administration of HS would contribute to correction of a hypovolemic state, rather than contributing to it.

Effects of HSS on mean ICP wave amplitude in SAH patients

Bed-side measurement of single wave intracranial pulse pressure is available based on a method developed by Per Kristian Eide at our institution (Eide, 2006a). This is an interesting variable, given the methodological problems with mean ICP discussed previously, and the
emerging documentation that mean ICP wave amplitude (intracranial pulse pressure) is better correlated with outcome than mean ICP (Eide and Sorteberg, 2006; Eide, 2006c; Eide et al., 2007b).

The measurement of intracranial pulse pressure is not a new thing. The fundamental difference in the new algorithm is that mean ICP wave amplitude is calculated based on exact measurements of single waves generated by each cardiac beat. Previous technologies have either only measured maximum and minimum ICP during a given time frame, e.g. 15 – 20 seconds, the results thus “contaminated” by e.g. the effects of the respiratory cycle on the ICP curve, or calculated on the basis of Fast Fourier transformation.

One important finding in Study III is that there is no correlation between the amplitude of ICP and the amplitude of systemic arterial blood pressure (ABP). We can therefore conclude that mean ICP wave amplitude is an independent variable reflecting the response to intracranial volume changes induced by each cardiac beat, i.e. a reflection of the intracranial compliance.

The main finding of Study III was that mean ICP wave amplitude was attenuated by HSS. This has to my knowledge not been demonstrated before. However, the effect on mean ICP wave amplitude was not directly comparable to the effect on mean ICP. First, there was not a good agreement between the two measurements, signifying that the value of one of them can not be deduced from the other. Secondly, there was a great discrepancy in target achievement between the two variables. “Normal” mean ICP wave amplitude was only achieved in a minority of cases while “normal” mean ICP was achieved in a majority of cases. This suggests that the intracranial compliance state was less favourable than expected from mean ICP in a majority of these patients. This is in concordance with the clinical perception we have from our clinical day to day practice in the ICU, that a mean ICP of < 15 mmHg is not “good enough” for a number of our SAH patients. For example, the mean ICP may be
normal, but the patient does not wake up. Only upon further reduction in mean ICP e.g by increasing CSF drainage, does the patient wake up. This is illustrated by a case report by Eide et al. where a SAH patient with normal mean ICP still was not waking up after 44 days (Eide et al., 2007c). Only after changing to an ICP-wave guided management which brought about increased CSF drainage, did the patient wake up. The notion that increased mean ICP wave amplitude is indicative of an unfavourable state, is also supported by another case report by Eide et al. that showed how increased amplitude was associated with increased levels of brain metabolites indicative of ischemia (Eide et al., 2007a). All this challenges the thought that “normal” mean ICP has the same implications in the injured and non-injured brain. These are interesting aspects deserving further attention in the future.

A positive spin-off effect of measuring mean ICP wave amplitude with an online display of the actual ICP curve drawn on the basis of measurements at 100 Hz, is that one has a useful tool for judging whether the ICP measurement is valid. The diagnosis of a partly dislodged catheter can readily be made just by looking at the curve. And in addition the system will classify the measurements as invalid. This is information not supplied by mere mean ICP.

**Future clinical research questions**

Reporting short time effects of hypertonic saline (HS) on intracranial pressure (ICP) variables in subarachnoid haemorrhage (SAH) patients is important, but to link the use of HS or measurements of increased mean ICP wave amplitude to effects on outcome; that is the real challenge.

- Further studies are needed to better enlighten many aspects related to the use of hypertonic saline in SAH patients with intracranial hypertension:
- Optimal dose
- Bolus, continuous infusion, or a combination
- Rebound phenomenon
- Timing related to time since injury
- Safety issues related to serum sodium levels and adverse effects

- Interesting and valuable knowledge would presumably emerge from studies combining metabolic changes measured with micro dialysis, cerebral water content and cerebral blood flow derived from MRI-investigations, and intracranial pressure variables during administration of hypertonic saline.

- There is an immediate need for more data relating mean ICP and mean ICP wave amplitude to neurological outcome.
MAIN CONCLUSIONS

All conclusions relate to patients suffering from acute spontaneous subarachnoid haemorrhage (SAH) investigated in the intensive care setting.

1. Intravenous bolus infusion of 7.2% (72 mg/mL) saline in 6% (60 mg/mL) hydroxyethyl starch 200/0.5 solution (HSS) during 20 – 30 minutes reduced intracranial pressure (ICP), both mean ICP and mean ICP wave amplitude, and increased cerebral perfusion pressure (CPP).

2. Intravenous bolus infusion of normal saline (single blind placebo) had no effect on mean ICP or CPP, verifying stable study conditions.

3. When HSS was infused as a bolus during 20 to 30 minutes, the reduction in mean ICP started almost immediately, but reached its maximum 20 to 30 minutes after the end of the infusion, thereafter tapering off, but without a rebound within 3 hours.

4. When mean ICP was above 20 mmHg, 2 mL/kg of HSS (2.46 mmol Na+/kg) reduced mean ICP in average by more than 50% at time of maximum effect, and mean ICP remained below baseline three hours later.

5. Changes in mean ICP were inversely related to changes in serum sodium levels, and mean maximum increase in serum sodium was about 6 mmol/L after 2 mL/kg of HSS.

6. A bolus infusion of 2 mL/kg of HSS increased cardiac output in our patients.

7. There was poor agreement between mean ICP and mean ICP wave amplitude, so the level of one variable cannot be deduced from the other for any given individual patient.

8. When the target level for mean ICP was reached after HSS infusion, the target for mean ICP wave amplitude was reached only in a few patients. This suggests that the
intracranial compliance may be less favourable than expected in many SAH patients with normal mean ICP and CPP.

9. There was no correlation between mean ICP wave amplitude (intracranial pulse pressure) and systemic arterial pulse pressure. This supports the view that mean ICP wave amplitude is reflecting the pressure response to intracranial volume changes induced by each cardiac beat, i.e. intracranial compliance.
IMPLICATIONS FOR CLINICAL PRACTICE

The studies included in this thesis have documented that intravenous infusion of HSS has a reliable effect on increased mean ICP in SAH patients. Mean ICP is lowered and as a consequence of that, CPP is increased. Based on the findings of this thesis, which are supported by other published studies, I now find there is enough evidence to recommend the use of HS for osmotherapy in SAH patients, as an alternative to or a supplement to mannitol.

In clinical practice, the mode of administration could preferably be modified compared with the regime presented in this thesis. The findings from study I indicates that a bolus dose could be reduced from the 2 mL/kg of HSS used in the study, and in clinical practice, an infusion time of 20 to 30 minutes would be perceived as too long. Further, our studies show how the positive effects on the ICP variables are gradually reduced as serum sodium returns to pre-infusion levels. I would therefore recommend to give a bolus of HS, e.g. NaCl 1 – 2 mmol/kg during 5 – 15 minutes, when ICP > 20 mmHg and osmotherapy is indicated, followed by a continuous infusion to maintain the serum sodium level achieved after the bolus. When needed, a new bolus can be administered, and the infusion continued to maintain the new sodium level. Since serum sodium in our studies increased by about 6 mmol/L after 2.5 mmol/kg, there is room for repeated boluses per day without increasing serum sodium more than 15 mmol/L/day. The inverse relationship between serum sodium and mean ICP, also teaches us that a careful tapering of a hypernatremic state is important and necessary to avoid rebound increase in mean ICP.

In our patients, cardiac output increased after HSS. This is in most cases clearly beneficial, as many of these patients require vasopressors to achieve a satisfactory haemodynamic situation. HSS may therefore reduce the need for such drugs.
It was not within the scope of this thesis to define the role of mean ICP wave amplitude in clinical practice. More research is needed, but the findings from Study III have taught us that the intracranial compliance situation is not necessarily good even though mean ICP and CPP is normal. So at least in the cases where the radiology findings are fine, mean ICP and CPP are fine, but the clinical state of the patient is not fine, these results lend support to actively try to improve intracranial compliance e.g. by infusion of HS or by increasing CSF drainage.
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