Quality systems to avoid secondary brain injury in neurointensive care

LENA NYHOLM
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Abstract

Outcome after traumatic brain injury (TBI) depends on the extent of primary cell death and on the development of secondary brain injury. The general aim of this thesis was to find strategies and quality systems to minimize the extent of secondary insults in neurointensive care (NIC).

An established standardized management protocol system, multimodality monitoring and computerized data collection, and analysis systems were used.

The **Uppsala TBI register** was established for regular monitoring of NIC quality indexes. For 2008-2010 the proportion of patients improving during NIC was 60-80%, whereas 10% deteriorated. The percentage of ‘talk and die’ cases was < 1%. The occurrences of secondary insults were less than 5% of good monitoring time (GMT) for intracranial pressure (ICP) > 25 mmHg, cerebral perfusion pressure (CPP) < 50 mmHg and systolic blood pressure < 100 mmHg. Favorable outcome was achieved by 64% of adults.

**Nurse checklists** of secondary insult occurrence were introduced. Evaluation of the use of nursing checklists showed that the nurses documented their assessments in 84-85% of the shifts and duration of monitoring time at insult level was significantly longer when secondary insults were reported regarding ICP, CPP and temperature. The use of nurse checklist was found to be feasible and accurate.

A **clinical tool to avoid secondary insults related to nursing interventions** was developed. Secondary brain insults occurred in about 10% of nursing interventions. There were substantial variations between patients. The risk ratios of developing an ICP insult were 4.7 when baseline ICP ≥ 15 mmHg, 2.9 when ICP amplitude ≥ 6 mmHg and 1.7 when pressure autoregulation ≥ 0.3.

**Hyperthermia**, which is a known frequent secondary insult, was studied. Hyperthermia was most common on Day 7 after admission and 90% of the TBI patients had hyperthermia during the first 10 days at the NIC unit. The effects of hyperthermia on intracranial dynamics (ICP, brain energy metabolism and $B_{T}pO_{2}$) were small but individual differences were observed. Hyperthermia increased ICP slightly more when temperature increased in the groups with low compliance and impaired pressure autoregulation. Ischemic pattern was never observed in the microdialysis samples. The treatment of hyperthermia may be individualized and guided by multimodality monitoring.

**Keywords:** Traumatic brain injury, Subarachnoid hemorrhage, Intracranial pressure, Quality register, Checklist, Nursing interventions, Pressure autoregulation, Intracranial compliance, Hyperthermia, Cerebral energy metabolism, Microdialysis and Brain tissue oxygenation.

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"No head injury is too severe to despair of, nor too trivial to ignore."

Hippocrates
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

**Paper I**
Nyholm L, Howells T, Enblad P, Lewén A.
Introduction of the Uppsala traumatic brain injury register for regular surveillance of patient characteristics and neurointensive care management including secondary insult quantification and clinical outcome.

**Paper II**
The use of nurse checklists in a bedside computer-based information system to focus on avoiding secondary insults in neurointensive care.
*ISRN Neurology* 2012;2012:903954.

**Paper III**
Nyholm L, Steffansson E, Fröjd C, Enblad P.

**Paper IV**
Nyholm L, Howells T, Enblad P.
A decision-making tool to prevent secondary ICP-insults related to nursing interventions – Evaluation of the predictive value for baseline ICP, compliance and autoregulation.
Submitted.

**Paper V**
Nyholm L, Howells T, Lewén A, Hillered L, Enblad P.
The effects of hyperthermia on intracranial pressure, cerebral oxymetry, and cerebral metabolism in traumatic brain injury patients during neurointensive care.
Submitted.

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<tbody>
<tr>
<td>ATLS</td>
<td>Advanced trauma life support</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
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<tr>
<td>B_{tp}O_{2}</td>
<td>Brain tissue oxygen pressure</td>
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<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
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<td>CBV</td>
<td>Cerebral blood volume</td>
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<td>CPP</td>
<td>Cerebral perfusion pressure</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>CVP</td>
<td>Central venous pressure</td>
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<tr>
<td>ECG</td>
<td>Electrocardiography</td>
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<td>GCS</td>
<td>Glasgow coma scale</td>
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<td>GCS-M</td>
<td>Glasgow coma scale motor response</td>
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<tr>
<td>GLP</td>
<td>Good laboratory practice</td>
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<td>GMT</td>
<td>Good monitoring time</td>
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<tr>
<td>GOS</td>
<td>Glasgow outcome scale</td>
</tr>
<tr>
<td>GOSE</td>
<td>Extended Glasgow outcome scale</td>
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<tr>
<td>GR</td>
<td>Good recovery</td>
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<tr>
<td>Hb</td>
<td>Hemoglobin</td>
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<tr>
<td>ICH</td>
<td>Intracerebral hematoma</td>
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<tr>
<td>ICP</td>
<td>Intracranial pressure</td>
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<tr>
<td>ISO</td>
<td>International organization for standardization</td>
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<tr>
<td>L/P ratio</td>
<td>Lactate/Pyruvate-ratio</td>
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<tr>
<td>Abbreviation</td>
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<td>--------------</td>
<td>------------------------------------------</td>
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<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
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<tr>
<td>MD</td>
<td>Moderate disability</td>
</tr>
<tr>
<td>NIC</td>
<td>Neurointensive care</td>
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<td>NWT</td>
<td>Neurological wake-up test</td>
</tr>
<tr>
<td>pCO₂</td>
<td>Carbon dioxide partial pressure</td>
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<tr>
<td>pO₂</td>
<td>Oxygen partial pressure</td>
</tr>
<tr>
<td>PRx</td>
<td>Pressure reactivity index</td>
</tr>
<tr>
<td>RLS</td>
<td>Reaction level scale</td>
</tr>
<tr>
<td>SAH</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>Severe disability</td>
</tr>
<tr>
<td>SjvO₂</td>
<td>Jugular venous oxygen saturation</td>
</tr>
<tr>
<td>TBI</td>
<td>Traumatic brain injury</td>
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<td>VS</td>
<td>Vegetative state</td>
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INTRODUCTION

Traumatic brain injury (TBI) is a substantial health problem with both high morbidity and mortality (1). Patients with TBI have a primary injury causing cellular damage. The outcome depends partially on the amount of primary cell death and also on the development of secondary brain injury. It is well known that primary injury initiates different injury cascades which will cause secondary brain injury (2, 3). Secondary brain injury may also be caused by secondary clinical insults (2). The importance of avoiding secondary clinical insults, e.g. high intracranial pressure (ICP), low cerebral perfusion pressure (CPP) and high temperature, after TBI was recognized in the 1970s (4). The concept of putting maximal focus on avoiding secondary insults causing secondary brain injury in TBI has been generalized to other acute brain injuries, e.g. subarachnoid hemorrhage (SAH) and spontaneous intracerebral hematoma (ICH). This concept was found to be even more important for further improvements in outcome after the failure of clinical trials with neuroprotective drugs (5-8). To this end, a secondary insult prevention program was introduced in the neurointensive care (NIC) unit at the department of neurosurgery in Uppsala in the 1990s (9). Implementation of the secondary insult prevention program led to a substantial improvement in outcome (9). One cornerstone in the secondary insult program was the creation of a standardized management protocol system based on good laboratory practice (GLP) principles (10) that was developed and maintained by the physicians and nursing staff in a collaborative effort. It is the nurses’ responsibility to monitor and observe whether a secondary insult occurs and to interrupt it adequately (11). When caring for patients at a NIC unit, preventive nursing interventions are performed to prohibit secondary insults but can also result in a secondary insult. Increased stress and decreased venous outflow are the two main reasons for elevated ICP during nursing interventions (12, 13). The timing of nursing interventions influences the risk of inducing secondary insults (14).

The general aim of this thesis was to find strategies and quality systems to minimize the amount of secondary insults and thereby optimize the care and treatment for TBI patients and other patients with acute brain injury in the NIC unit.
History of neurosurgery and neurointensive care

Archaeologists in Europe have found craniums with marks after trepanations from 3000 years before Christ. One of the early pioneers of surgery was Peter Lowe (1550-1612). He was the first to write about methods of several different neurosurgical procedures, and he also made illustrations of the tools he used for surgery (15).

During the polio epidemic of 1952 in Copenhagen, Denmark, Bjorn Ibsen was the first to use positive pressure ventilation outside the operation theatre treating polio patients without spontaneous breathing (16). The patients were ventilated by a cuffed tracheostomy and sedated (16). Dr. Ibsen had an idea of a specialized ward for all critically ill patients and the first intensive care unit was founded in December 1954 (17, 18). In the early 1960s Max Harry Weil established the first “shock ward” and he is consequently called “the father of modern intensive care” (17). The development of intensive care made it possible to treat patients with TBI in a more active way. In the mid-1980s the first NIC units were started (19). Central for this kind of units is specialized neuroscience nurses and physicians (19). Some studies indicate that TBI patients treated at a NIC unit have decreased mortality, improved outcome and shortened hospital stay than TBI patients treated at a general intensive care unit (19-22).

Epidemiology

TBI is a substantial health and socioeconomic problem worldwide. In countries with a high economic standard, TBI is the leading cause of death and disability among young people (23, 24). The incidences vary in reports due to different sources of data, methods of calculation and assumptions (24, 25). Generally males are at higher risk for TBI especially in adolescence and young adulthood (24). TBI occurs at a higher frequency from puberty to young adulthood and among the elderly (24). The incidence of hospitalized or fatal TBI in the European Union is approximately 235 per 100,000 and year, in Finland 101 and in the U.S. 150-250 per 100,000 and year (24-26). In these rich countries, TBI caused by fall accidents is rising among elderly people (1, 27). In poor countries, the incidence of TBI is escalating because
of the increasing use of motor vehicles (28). Because of the long rehabilitation period after TBI and sometimes lifelong sequelae the prevalence is considerably higher than the incidence. For example the prevalence in the U.S. is reported to be 1893 per 100,000 (26).

Physiology and pathophysiology

The cranial cavity in an adult comprises 80% brain, 10% blood and 10% cerebrospinal fluid (CSF). This was found out by Monro in 1783 (29) and Kellie in 1824 (30). Because the cranial cavity cannot expand, the total intracranial volume remains constant. If the volume in one compartment increases or a new mass lesion appears, it first leads to a decrease in the volume of the other compartments. Once these intracranial compensatory mechanisms are exhausted a small increase in volume causes a large increase in ICP (13). This can be illustrated with the volume/pressure curve (Figure 1). The shape of the volume/pressure curve was discovered by Ryder (31) and later Marmarou (32) confirmed that Δ volume/Δ pressure creates the slope of the curve or compliance. Compliance is a measure of the adaptive capacity of the brain to preserve intracranial equilibrium despite physiological and external changes (33). Factors that can influence the adaptive capacity are the amount and time of volume increase (33).

![Figure 1. The volume/pressure curve](image-url)
Cerebral blood flow

In normal conditions the brain uses about 15% of the cardiac output and about 20% of the total oxygen uptake in the body (34-36). The global rate of oxygen consumption is 160 μmol/100 g brain and minute. Lack of oxygen supply is called hypoxia. The definition of hypoxia is a reduction in tissue oxygen partial pressure (pO₂) to levels insufficient to maintain cellular function (36). Normal cerebral blood flow (CBF) is on average 50 ml/100 g brain and minute (35, 37). This supply cannot be interrupted; a few seconds of circulatory arrest causes unconsciousness and a few minutes induces irreversible damage to the brain (34, 38). More exactly a CBF of 15-20 ml/100 g brain and minute causes reversible neural dysfunction, whereas a CBF of 10-15 ml/100 g brain and minute causes irreversible neuron damage in a time-dependent manner (Figure 2) (37-40). Ischemia is described as the reduction of blood flow that can result in interrupted oxygen supply and accumulation of metabolic products, for example increased carbon dioxide partial pressure (pCO₂) and lactic acid (35). Cerebral ischemia is probably the most important pathological problem connected with TBI (36). If ischemia is not treated it causes an infarction of the brain. Bouma et al. (1991) found significantly lower CBF during the first 4-6 hours after trauma than on any later examination (41). The CBF was below 18 ml/100 g brain and minute in 33% of the patients in the first examination. The occurrence of low CBF during the first hours after trauma was found to correlate to clinical status and outcome to a high extent (41).

![Figure 2. Ischemia thresholds. Figure derived from Jones and colleagues (38).](image-url)
Regulation of cerebral blood flow
In order to supply the brain with blood in accordance with its functional or metabolic needs three main mechanisms of autoregulation are described in the literature (35).

**The myogenic hypothesis, pressure autoregulation** The arterioles and small arteries constrict or dilate as a response to an increase or decrease in the transmural pressure gradient (35).

**The metabolic hypothesis** Increasing metabolic demands increases cerebral blood flow and vice-versa. pCO₂ is a strong factor in the regulation of CBF (35, 36, 42).

**The neurogenic hypothesis** The blood vessels are innervated by both cholinergic, adrenergic and aminergic nerves (34, 35).

*Cerebral blood flow pressure autoregulation*
Pressure autoregulation could be described as CBF remaining relatively constant despite variations of MAP (Figure 3) (34). Pressure autoregulation ensures the supply of oxygen, and energy substrate to the brain tissue is constant when the mean arterial pressure (MAP) changes from about 50 mmHg to about 150 mmHg in a healthy brain (43, 44).

*Figure 3. Pressure autoregulation.*
The upper and lower limits of pressure autoregulation should not be considered as absolute (34, 35). Pressure autoregulation could be impaired or absent in various situations, for example severe hypocapnia, hypoxia or TBI (Figure 4) (34, 44). There is a wide spectrum of the degree of impaired pressure autoregulation and an irregular distribution of the impairment in the injured brain (37). In patients with severe TBI 49-87% had impaired or no pressure autoregulation (37). These patients have higher risk of developing cerebral ischemia if hypotension occurs (37). Patients with impaired pressure autoregulation are more likely to have unfavorable outcome (45-47). Patients with impaired pressure autoregulation have better outcome if they are treated with normotensive ICP-oriented therapy (48). The third edition of Guidelines for Management of Severe Traumatic Brain Injury states, that patients with intact pressure autoregulation may tolerate higher CPP values (49).

Figure 4. No pressure autoregulation.

Cerebral Metabolism
The brain uses the same principles for energy metabolism as the rest of the body but it has some unique features (34). The brain has its own chemical environment because of the blood brain barrier, it has high energy demands and very limited glycogen stores (covers 1-3 minutes of neuronal function with complete cessation of CBF) (50, 51). Glucose utilization is 30 μmol/100 g brain and minute (35, 36). Cerebral tissue glucose content is approximately 30% of plasma glucose concentration (36).
Glucose is the main fuel for the brain and it is oxidized according to the equation (35, 44):

\[ C_6H_{12}O_6 + 6 \text{ O}_2 \rightarrow 6 \text{ CO}_2 + 6 \text{ H}_2\text{O} + 34-36 \text{ ATP} \]

More than 90% of the oxygen delivered to the brain is used by the mitochondria to generate adenosine triphosphate (ATP) (51). Aerobic metabolism generates 18 times more energy than anaerobic glycolysis (Figure 5) (44, 51, 52).

*Figure 5. Aerobic and anaerobic metabolism.*
Energy is used to maintain the ionic gradients across the cell membranes. During ischemia the glycolysis occurs 7-8 faster and all the glucose, glycogen and ATP are consumed within one minute (44, 51). Cerebral oxygenation depends on three factors: CBF, arterial content of oxygen and cerebral metabolic rate of oxygen (53). The brain tissue oxygenation (B\textsubscript{tip}O\textsubscript{2}) depends on the oxygen dissociation curve. High temperature, high \textit{pCO}_2 and metabolic acidosis decrease the \textit{O}_2 affinity of hemoglobin (Hb) which leads to elevated B\textsubscript{tip}O\textsubscript{2} (54).

There are three patterns of biochemical changes due to brain injury that could be seen in microdialysis and B\textsubscript{tip}O\textsubscript{2} monitoring (55, 56).

**Ischemia** An interruption of CBF $\rightarrow$ decrease in B\textsubscript{tip}O\textsubscript{2} $\rightarrow$ rapid increase in lactate and decrease in pyruvate $\rightarrow$ increased lactate/pyruvate-ratio (L/P ratio). Because of the interrupted CBF the delivery of glucose is ended $\rightarrow$ pyruvate decreases to a very low level.

**Metabolic crisis/Mitochondrial dysfunction** The delivery of oxygen and glucose is unchanged. Due to mitochondrial dysfunction or excessive increase in metabolic requests e.g. seizures the oxidative metabolism is not able to meet the energy demands. This leads to increased lactate and normal to slightly increased levels of pyruvate $\rightarrow$ increased L/P ratio. Metabolic crisis occurred in 74% of TBI patients in the first days after trauma and is associated with poor outcome. If the metabolic crisis is associated with mitochondrial dysfunction B\textsubscript{tip}O\textsubscript{2} is stable or increased. (56).

**Arousal/Hyperglycolysis** The increased energy consumption $\rightarrow$ increased oxidative metabolism $\rightarrow$ lactate and pyruvate are both increased $\rightarrow$ L/P ratio is stable. B\textsubscript{tip}O\textsubscript{2} increases due to increased CBF.

**Primary and secondary injury**

TBI is a heterogeneous disorder with several different types of presentation due to the force that caused the injury. TBI patients acquire a primary brain injury at the time of the accident causing cellular damage. It is the nature, intensity, direction and duration of these forces that determine the primary injury (1). Cell death continues for several days after the primary injury and is called secondary brain injury.
Different mechanisms/cascades are involved in the development of secondary brain injury (3):

- Oxidative stress
- Inflammation
- Blood-brain barrier disruption
- Necrosis/Cell death
- Mitochondrial dysfunction
- Excitotoxicity

Researchers in Glasgow during 1968-1972 studied a group of TBI patients who talked after the accident and later died, to understand the poor outcome (4). The study led to the first knowledge about the importance of avoiding secondary clinical brain insults (4). Secondary clinical insults can be both systemic (e.g. hypoxia, hypercapnia and hypotension) and intracranial (e.g. intracranial hypertension, seizures and vasospasm) (2). Both the primary injury and the secondary clinical brain insults initiate secondary brain injury cascades (3) (Figure 6). These secondary insult cascades are interactive and may occur simultaneously (3). The extent of secondary brain injury strongly influences patient outcome (Figure 6) (57).

Figure 6. Outline of how primary and secondary injury interact and lead to outcome.

Prehospital care

After the injury, prehospital and primary hospital care of the TBI patient should follow the Advanced Trauma Life Support (ATLS®) recommendations to guarantee adequate ventilation and circulation (58). Patients unable to follow commands should be intubated if possible. The prehospital management of TBI patients should focus on stabilization of vital signs and immediate transport to hospital (59). Avoidance of secondary insults is essential for both short- and longtime outcome (60).
Neurointensive care

The main focus when treating and caring for TBI patients in a NIC unit is to avoid secondary insults, both systemic and intracranial. Therefore neuromonitoring as well as monitoring of vital parameters are the most important tasks (61). European and American guidelines are available for the NIC management of TBI (61, 62) and the recommendations are as follows. ICP monitoring should be considered in all patients not responding to commands, Glasgow Coma Scale Motor response (GCS-M) ≤ 5. A ventricular drainage system should be used if possible, but in cases with a compressed ventricular system a parenchymal probe can be used instead (62). All patients who do not respond to commands, GCS M ≤ 5 should be intubated and artificially ventilated. Moderate hyperventilation with a pCO₂ 4.0-4.5 kPa can be applied temporarily but should then gradually be adjusted towards normoventilation under surveillance of ICP (61, 63). To reduce pain and stress, TBI patients should receive sedation and pain relief (64). Stress, pain and discomfort can contribute to increases in ICP among TBI patients and should be avoided. Propofol or midazolam are the most used sedative agents in TBI patients (64) and are reportedly similarly safe and efficient (65-67). Propofol has a rapid onset and short duration of action and therefore use of propofol facilitates neurological wake-up tests (NWT). Furthermore it depresses cerebral metabolism and oxygen consumption (64). If ICP remains elevated despite this basal treatment, evacuation of space occupying mass lesions, CSF drainage, tiopenthal coma treatment and external decompressive craniectomy can be used (68). In cases with high ICP, mannitol (a sugar solution used as an osmotic diuretic) or hypertonic sodium solutions could also be used to lower the ICP quickly and effectively (69, 70).

All patients at the NIC unit should have the upper body raised 30-45° in order to prevent ventilator associated pneumonia (71). This body position may also facilitate venous outflow from the brain and thereby decrease ICP (72).

Nursing interventions

Patients at a NIC unit are frequently cared for in different ways throughout the day and night (Figure 7). In a qualitative study NIC nurses were asked to identify different nursing interventions they made the last time they cared for a TBI patient (73). The answers were grouped in four categories:
Neuro-physiological interventions: e.g. monitoring general and neurophysiological parameters, administration of medicines, ventilator management and monitoring fluid status, all with the purpose of avoiding secondary brain injury.

Injury prevention interventions or preventing complications: e.g. turning/repositioning, hygienic measures, reorienting the patient and fall prevention.

Maintaining therapeutic milieu: limit stimuli, e.g. light, noise, visitors and space nursing activities.

Psychological intervention: e.g. family support.

All nursing interventions are made with the aim to benefit the patient; for example oral care and endotracheal suction is made to prevent lung failure. When caring for patients at a NIC unit, nursing interventions can lead to a secondary insult and it is the nurses’ responsibility to monitor and observe whether a secondary insult occurs and to interrupt it adequately (11). A study aimed at determining which physiological and situational variables influenced the NIC nurses’ judgment found that significant predictors were oxygen saturation, ICP and CPP (74). The same author also analyzed how the individual nurse characteristics affected the judgment about risk for secondary insults and found that time of day and number of years in intensive care unit significantly influenced the judgment (75). The timing of nursing interventions influences the risk for secondary insults (14). It is the nurses’ obligation to achieve a balance between prevention of secondary insults and nursing interventions. This balance gives the patient the best possibility to recover (76).
Oral care seems not to affect ICP among TBI patients (77, 78) and tooth brushing manually or by electric means has similar effect (79).

It is known that repositioning increases the risk for secondary insults (80) but there is no single body position that is most hazardous (81). For most patients both supine and prone positions are suitable considering ICP, CPP and MAP. Prone position increases pO$_2$, arterial oxygen saturation and respiratory system compliance (82, 83). The effects of backrest position are discussed. Elevation of the head 30° decrease ICP but it may also decreases CBF and no consensus exist (72).

Performing endotracheal suction also increases the risk for secondary insults (80) but this risk can be decreased if the patient is properly sedated (84). One way to reduce the risk for secondary insults in connection with nursing interventions is to allow enough time between the interventions for the patients to return to their baseline ICP (80).

TBI patients have general metabolic changes that increase the energy demands substantially during the first 30 days postinjury (85). Several guidelines recommend early initiation of enteral feeding (within 24-48 h of admission) and that full energy requirement should be administered by day seven postinjury (85).

**Multimodal monitoring**

TBI patients need both general physiological monitoring of e.g. circulation and respiration, and specific neuromonitoring (Figure 8).

The nurse at a NIC unit has an important task in surveillance and following all physiological parameters and the TBI patients’ responses to sedation, as well as other medical treatment and nursing procedures (86).
General physiological monitoring

General monitoring in TBI patients includes the following: electrocardiography (ECG), pulse oximetry, arterial blood pressure (arterial catheter), central venous pressure (CVP), continuous systemic temperature, urine output, arterial blood gases (e.g. pH, pO₂, pCO₂, Hb and electrolytes) body temperature, and other regular blood samples (87).

Systemic oxygenation and blood pressure

In the third edition of Guidelines for Management of Severe Traumatic Brain Injury the recommendation is that oxygenation should be monitored and hypoxia (arterial oxygen saturation < 90%) avoided. Moreover, it is recommended that blood pressure should be monitored and hypotension (systolic blood pressure (SBP) < 90 mmHg) should be avoided (88).

Body temperature

Hyperthermia is very common in TBI patients. The incidence is reported to be 15-80% (89-94). There are three different reasons why these patients develop fever:

- Infections
- Noninfectious fever e.g. neurogenic fever
- Hyperthermia syndromes
The most common reason for fever in TBI patients is from pulmonary infections (95). Indicators of noninfectious neurogenic fever are early onset (within 72 hours) and long duration (96). It is well described that fever decreases outcome, increases mortality and prolongs the hospital stay for TBI patients but there is no evidence showing that treating fever is beneficial (95, 97-99).

Most of the existing guidelines on TBI patients recommend maintenance of normothermia, but there are few recommendations on how to do this (100). However, reportedly hypothermia reduces high ICP in patients with severe TBI (96).

Pharmacological interventions to reduce fever are common. Paracetamol is often used but it can be associated with hepatic toxicity as a side-effect (95). The next step in fever treatment is external cooling with water-circulating cooling blankets (97). One side-effect of fever reduction is shivering (95, 97). Hata et al. (2008) have studied changes in systemic oxygen consumption in TBI patients treated with therapeutic normothermia using a surface-cooling device. The patients who developed shivering had no significant reduction in systemic oxygen consumption after temperature reduction. Patients who did not develop shivering had significant improvement in systemic oxygen consumption (101). A small study with 15 patients found that shivering significantly decreases the $B_i\text{pO}_2$ and that the magnitude of shivering is associated with the degree of decreased $B_i\text{pO}_2$ (102). Treating fever may also hide the symptoms of an infection and therefore delay treatment of infections (95).

It is the bedside nurses at the NIC unit that monitor the body temperature and recognize and treat fever (95). A study by Thompson et al. (2007) found a high incidence of fever among TBI patients and that it is undertreated by nurses (89).

There is only one article in the Cochrane Collaboration about body temperature and TBI. It concluded that there are no randomized, controlled clinical trials of modest cooling therapy (35-37.5°C) after TBI that have reported any improvement in outcome. Therefore, modest cooling therapy after TBI cannot be recommended at present (103).

**Neuromonitoring**

There are several types of neuromonitoring divided into three groups: intracranial pressure monitoring, cerebral oxygenation monitoring, cerebral metabolism and biochemistry monitoring.

These different types of monitoring are often used in combination with the purpose of avoiding weaknesses of each technique and of achieving a more confident way in detecting secondary insults (104).
ICP

The development of the technique of external ventricular drainage took place in 1850-1908 (105). In 1951, Guillaume and Janny used continuous graphic recording of ICP in a study in patients with surgical diseases (106). Nils Lundberg was the first to measure ICP continuously and to document it graphically in ordinary neurosurgical patients in 1960 (107).

Today international guidelines recommend that all patients who do not respond to commands or have an abnormal computed tomography (CT) scan should have ICP monitoring (108). When monitoring ICP, intraventricular catheters are regarded as the golden standard. The ventricular catheters allow calibration in vivo and provide access to the ventricular system which also allows CSF drainage if the ICP increases (1, 23, 109). If the brain is edematous and the ventricles are narrow, an intraparenchymal catheter is often chosen (109). Treatment should be started if ICP increases above 20 mmHg (108). High ICP is an strong indicator of prognosis and is associated with worse outcome (4, 98). Potential complications of ICP-monitoring are infections, hemorrhages or malpositioning of the probe (87). One randomized study compared ICP monitoring with clinical/imaging examinations found that the outcome of both methods did not significantly differ (110). This trial has then been criticized by some other researchers (111, 112).

The standardized management protocol at the NIC unit in Uppsala states that patients who do not obey commands should have ICP monitoring and the threshold is less than 20 mmHg (113).

Cerebral perfusion pressure

CPP is equal with MAP minus ICP. CPP is often used to estimate CBF (13, 49, 53). It is unclear whether an artificially increased CPP will increase CBF and artificially increased CPP probably does not benefit outcome (49). In the third edition of Guidelines for Management of Severe Traumatic Brain Injury the recommendation is that CPP should be in the range of 50-70 mmHg (49). Even short duration (5 minutes) of low CPP (< 50 mmHg) are associated with poor outcome (114). Therapy provided in Lund, Sweden is based on reduction of ICP by lowering CPP to reduce the risk of vasogenic edema (115). A recommendation in the most recent brain trauma foundation guidelines states that CPP management should be based on pressure autoregulation status (49). Patients with preserved pressure autoregulation are more likely to have a favorable outcome even if CPP is in the higher range (48, 49).

Cerebral oxygenation

The jugular venous oxygen saturation (SjvO₂) and BtipO₂ measure cerebral oxygenation. SjvO₂ measures global cerebral oxygenation and BtipO₂
measures focal cerebral oxygenation (87). The thresholds for $SjvO_2$ is $< 50\%$ and for $B_{tip}O_2 < 15 \text{ mmHg}$ (116).

**Cerebral microdialysis**

Cerebral microdialysis is an established tool for neurochemical monitoring of patients with TBI (117). A microdialysis catheter has a fine double lumen probe with a tip made of semipermeable dialysis membrane. The tip is placed in brain tissue. A perfusion fluid is pumped through the catheter and collected for bedside analysis. Diffusion drives the passage of molecules across the membrane along their concentration gradient (118). Monitoring TBI patients with microdialysis can identify signals of cellular disturbance before clinical symptoms are manifesting (Table 1) (119, 120). Bedside cerebral microdialysis allows sampling and test results every hour (121).

**Table 1. MD biomarkers**

<table>
<thead>
<tr>
<th>Energy metabolism</th>
<th>Glucose, Lactate and Pyruvate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia</td>
<td>L/P ratio</td>
</tr>
<tr>
<td>Excitotoxicity</td>
<td>Glutamate</td>
</tr>
<tr>
<td>Cellular distress</td>
<td>Glycerol</td>
</tr>
</tbody>
</table>

**Compliance**

Intracranial compliance is the change in volume per unit change in ICP ($C = \Delta V/\Delta P$) (122). This can be illustrated by the volume/pressure curve (Figure 1) Decreased intracranial compliance may increase the risk for secondary brain injury (123, 124). For a long time it has been suspected that ICP pulse wave amplitude and morphology could estimate the cerebral compliance (125). In the clinical setting compliance can be evaluated as the height of the ICP amplitudes (Figure 9) (126). Mean ICP and ICP amplitudes are correlated to each other (127-129).

![Figure 9](image.png)

*Figure 9.* Compliance before (left) and after (right) craniectomy. The figure is from the Odin monitoring system and the time scale is in the bottom.
The pressure reactivity index

The pressure reactivity index (PRx) is a method to estimate the degree of pressure autoregulation. PRx is based on the correlation of ICP and MAP. High values of PRx are associated with poor autoregulation, and low values with intact autoregulation (45).

Neurological wake-up test

In order to evaluate a patient's neurological status and possible deterioration standardized scales are used, either the Reaction Level Scale (RLS) (130-132) or Glasgow Coma Scale (GCS) (133). When sedation was interrupted and NWT was performed in TBI patients ICP increased and CPP decreased slightly in most patients (134).

Quality assurance

Quality can be described and defined in many ways. The international organization for standardization (ISO) 9000, which is an international consensus on good quality management practice, states:

“... quality of something cannot be established in a vacuum. Quality is always relative to a set of requirements...”

Another description of quality is from the National Academy of Medicine, Washington, USA:

“The degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge. ”

Quality assurance in healthcare can be managed in several ways, for example with checklists, quality registers, by measuring clinical outcome and with guidelines.

Outcome

Several circumstances contribute to each TBI patient’s final outcome. In a systematic review of factors contributing to outcome in TBI patients, older age, male gender, lower level of education, lower GCS, no pupil reaction, findings on CT scan and duration of coma were significant prognostic factors (135). The extent of secondary injury substantially impacts outcome (57, 98). TBI patients receive a better outcome with multi-disciplinary rehabilitation (136).
TBI should be seen as a chronic disease with consequences that continues over many years or decades (137-139). One year after trauma a TBI patient is e.g. 37 times more likely to die from seizure and 4 times more likely to die from pneumonia (140).

In order to evaluate the results of the treatment of TBI patients a clinical outcome examination can be performed. The most widely implemented method to measure outcome for TBI patients is the Glasgow Outcome Scale (GOS) (Table 2) (133, 141). GOS is assigned after a short, often unstructured interview, not following a protocol. The scale focuses on how the injury has affected function overall (142). Studies comparing GOS to emotional and cognitive scales show that GOS made an appropriate overall summary of the outcome (143, 144).

*Table 2. Outline of Glasgow Outcome Scale (142).*

<table>
<thead>
<tr>
<th>GOS categories</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>D</td>
</tr>
<tr>
<td>Vegetative state</td>
<td>VS Unable to obey commands.</td>
</tr>
<tr>
<td>Severely disabled</td>
<td>SD Conscious but disabled</td>
</tr>
<tr>
<td>Moderately disabled</td>
<td>MD Independent but disabled</td>
</tr>
<tr>
<td>Good recovery</td>
<td>GR May have mild residual effects</td>
</tr>
</tbody>
</table>

GOS was criticized for having overly broad categories. In order to increase the reliability a structured interview was created to evaluate outcome, Glasgow Outcome Scale Extended (GOSE) (Table 3) (142, 145). GOSE consider consciousness, independence inside and outside home, work status, social activities, relationships with families and friends and return to normal lifestyle (145).
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td><strong>Vegetative state</strong> Unable to obey commands.</td>
</tr>
<tr>
<td></td>
<td><strong>Severely disabled</strong> Can obey commands. Is not independent in the home, needs frequent help almost all the time.</td>
</tr>
<tr>
<td></td>
<td>- lower</td>
</tr>
<tr>
<td></td>
<td><strong>Severely disabled</strong> Can obey commands. Is not independent in the home, can look after themselves for up to 8 hours.</td>
</tr>
<tr>
<td></td>
<td>- higher</td>
</tr>
<tr>
<td></td>
<td><strong>Moderately disabled</strong> Is independent in and outside of home (can shop and travel). Cannot work and/or almost unable to participate in social and leisure activities and/or has constant intolerable psychological problems.</td>
</tr>
<tr>
<td></td>
<td>- lower</td>
</tr>
<tr>
<td></td>
<td><strong>Moderately disabled</strong> Is independent in and outside of home (can shop and travel). Reduced work capacity and/or participates much less in social and leisure activities and/or has frequent tolerable psychological problems.</td>
</tr>
<tr>
<td></td>
<td>- higher</td>
</tr>
<tr>
<td></td>
<td><strong>Good recovery</strong> Is independent in and outside of home (can shop and travel) and has previous work capacity. Participates a bit less in social and leisure activities and/or occasionally psychological problems and/or other minor problems relating to the head injury.</td>
</tr>
<tr>
<td></td>
<td>- lower</td>
</tr>
<tr>
<td></td>
<td><strong>Good recovery</strong> Is independent in and outside of home (can shop and travel) and previous work capacity, no sequel from the head injury.</td>
</tr>
<tr>
<td></td>
<td>- higher</td>
</tr>
</tbody>
</table>
A weakness of most such scales is that they do not specify how to evaluate patients with psychological or physical problems before injury. GOSE consider the difference between the patients status before injury with the status when the follow-up interview is made (145). Nevertheless, it may be difficult to understand how life was before injury and what the difference between then and now is. For patients with TBI, the follow-up interview should be done after 6 months because most outcomes are stable at this time and only a few patients have been afflicted with a new disorder or trauma (145). In Uppsala the TBI patients get a telephone call for the follow-up interview after about 6 months.

Checklists
Checklists can have different areas of application, for example memory recall, standardization and regulation of processes or methodologies (146). It is important to select the best indication and to make easy, short checklists. If there are an overwhelming number of demanding checklists the users may give too much time to the checklists, which can threaten the speed and quality of care (146). If checklists are too demanding there is a risk of decreased compliance among users (146). A checklist is an easy way to prevent errors of omission in basic areas of intensive care (147, 148). Checklists have to be developed through literature reviews, current practices and with consideration of expert consensus (148).

Quality registers
Quality registers are used for different purposes for example longitudinal follow-up, evaluation of the impact of treatments both medically and economically and to collect data for future academic studies (149-152). Another application for quality registers is the possibility of identifying patients who did not have the expected results (153). It is necessary to establish rules for inclusion/exclusion for the register. This is done in two aspects, the person’s characteristics (in this case diagnosis) and place of residence (referral area) (154, 155). If too much data are missing, it is difficult to make correct conclusions based on register content (156). If a review of the register is made, it certainly leads to more data being included (157). Collecting data for a quality register is time-consuming and expensive.
Guidelines

National Academy of Medicine, Washington, USA, defined clinical guidelines as (158):

“Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.”

Guidelines must have scientific context and should be produced in a structured way (159, 160). Guidelines are able to achieve three goals (159, 161):

- Increase the quality of the care and treatment
- Ensure all patients get the same care and treatment
- Ensure efficiency in use of health care resources

Nevertheless, what is recommended in a guideline for patients overall may not be appropriate for individuals (161, 162). A properly written guideline offers flexibility in various clinical situations (163).

The introduction of guidelines in NIC is associated with improvement applying to outcome, mortality, and need for mechanical ventilation (9, 164-166).

Rationale for this thesis

TBI is a substantial health problem with high morbidity and mortality. Patients afflicted with TBI, their families and significant others are in a vulnerable situation and at the mercy of the personnel at the NIC unit. As a NIC nurse it is rarely possible to communicate with the patients in an ordinary way due to sedation and unconsciousness. Therefore the nurses have to take decisions on how to perform the best possible care for the patients by considering monitor data and analyzing possible physiological reactions. In order to improve the quality of NIC, it is important to study pathophysiology in relation to nursing interventions to be able to offer an even better care in the future. Secondary brain insults are the major threat for TBI patients during the stay at the NIC unit. Awareness of this threat is essential at all time during the stay at the NIC unit to acquire optimal outcome for every TBI patient. Quality systems may assist in achieving this goal.
AIMS

General aim
The general aim of this thesis was to find strategies to minimize the extent of secondary insults causing secondary brain injury and to optimize care and treatment of TBI patients and other patients with acute brain injury in the NIC unit.

Specific aims

Paper I
The aims of this paper were to present the design of the TBI register (a quality register at Uppsala clinical research center) and to demonstrate the functionality by reporting the first results from the register.

Paper II
To evaluate the feasibility and accuracy of using nurse checklists integrated in a bedside computer-based information system for documentation of secondary insults with the ultimate goal of getting maximal attention to avoid secondary insults in the NIC unit.

Paper III
To investigate the extent of secondary insults caused by different nursing interventions in a NIC unit with standardized care and maximum attention on avoiding secondary insults.

Paper IV
To study the risk of inducing high ICP in association with nursing interventions and to evaluate whether ICP amplitudes, baseline ICP level or PRx could be used to identify patients at risk of developing high ICP in association with a nursing intervention.

Paper V
To evaluate the relationship between hyperthermia and ICP, and determine whether intracranial compliance and CBF pressure autoregulation affected that relationship. To study the relations between hyperthermia and \( B_{\text{iPO}_2} \) and cerebral metabolism.
PATIENTS

Paper I
All 314 patients with TBI treated during 2008-2010 were included. The study contained 66 women and 248 men with an age of 0-86 years (mean 43 years). Out of these 314 cases, 33 were children aged ≤ 15 years (mean 9 years).

Paper II
All consecutive patients with TBI monitored with ICP, CPP and SBP for at least 7 days from 1 January 2008 to 31 October 2008 at the NIC unit were included in this study. A total of 26 patients, 5 women and 21 men, aged between 18-72 years (mean 39 years) were included.

Paper III
All consecutive neurosurgery patients older than 18 years who had ICP monitoring and were intubated more than 24 hours from 7 May 2011 to 28 June 2011 at the NIC unit were included in this study. A total of 18 patients, 7 women and 11 men, aged 36-76 years (mean 57 years) were studied. The diagnoses among these patients were SAH (n=8), TBI (n=4), ICH (n=3), malignant middle cerebral artery infarction (n=2) and thalamic infarction (n=1).

Paper IV
Twenty-eight patients, 4 women and 24 men, with TBI treated from 1 March 2012 to 22 August 2014 were studied. Inclusion criteria were: age 16-80 years, ICP monitoring (closed ventricular drainage or a parenchymal probe) and intubated. Patients with CSF leakage, tiopenthal coma treatment and/or external decompressive craniectomy were excluded from the study. Patients already having increased ICP > 20 mmHg were also excluded. The median age was 49 (range 19-79).

Paper V
All patients with TBI from 1 January 2008 to 31 December 2010 were included if they were mechanically ventilated and had ICP monitoring. The study included 103 patients, 20 women and 83 men. The median age was 41 years (range 15-80).
METHODS

Standardized neurointensive care management (Paper I-V)

The TBI patients are treated according to a standardized escalated management protocol (Figure 10) (9), which is based on available guidelines (61, 62, 64). The management is in most cases the same for patients with other acute brain injuries (167).

The standardized management protocol system developed at the NIC unit in Uppsala is based on the GLP principles and contains written instructions that describe all kinds of routines, i.e. standard operating procedures (10). The main objective is to make all staff members maximally aware that their main task is to avoid secondary insults. The treatment goals are described in the standardized management protocol system (Table 4).

Table 4. Treatment goals according to the standardized management system

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP</td>
<td>&lt; 20 mmHg</td>
</tr>
<tr>
<td>CPP</td>
<td>&gt; 60 mmHg</td>
</tr>
<tr>
<td>SBP</td>
<td>&gt; 100 mmHg</td>
</tr>
<tr>
<td>pO₂</td>
<td>&gt; 12 kPa</td>
</tr>
<tr>
<td>pCO₂</td>
<td>4.0-4.5 kPa</td>
</tr>
<tr>
<td>Temperature</td>
<td>&lt; 38°C</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>5-10 mmol/L</td>
</tr>
</tbody>
</table>

All patients who do not respond to command (GCS-M ≤ 5) should be intubated and artificially ventilated (sedated with propofol and morphinechloride) and ICP should be monitored. The reaction level is checked regularly. All TBI patients’ heads should be slightly elevated to facilitate venous outflow and to prevent ventilator associated pneumonia. Significant mass lesions should be evacuated. If ICP remains elevated despite this basal treatment, CSF drainage, tiopental coma treatment and external decompressive craniectomy are used in an escalated order, see Figure 10.
The standardized management protocol system also describes many other routines at the NIC unit, for example the importance of giving extra sedation and pain relief to the patients before and during a nursing intervention and how to perform nursing interventions e.g. oral care, endotracheal suction and hygienic measures.
Bedside computer-based secondary insult nurse checklists

After each work shift the nurses record whether there have been secondary insults or not during their shift by ticking a box for Yes or No for each of 8 insult categories in a checklist in the bedside computer-based information system (Figure 11). According to the standardized management system, presence of secondary insult was to be recorded if all regular treatment procedures outlined in the standardized management system had been performed and the patient still had not reached the treatment goals.

![Figure 11. The checklist recording of secondary insults in a bedside computer-based information system.](image)

Quantification of secondary insults and collection of monitoring data (Paper I-V)

All patients at the NIC unit in Uppsala are connected to the Odin monitoring system (168) developed by Tim Howells and colleagues in Edinburgh and Uppsala. This system collects minute-by-minute monitoring data and makes it possible to study physiological monitoring parameters in real time or retrospectively. The quality of the monitoring data was screened and clear artifacts removed using the Odin software. The monitoring time remaining after artifact removal and exclusion of gaps in monitoring data associated with e.g. radiology examinations or surgical procedures was defined as Good Monitoring Time (GMT). The extent of secondary insults was calculated as the proportion of GMT spent above/below defined insult levels (Paper I-II,V).
Monitoring parameters

ICP (Paper I-V)
ICP was monitored with a ventricular drainage catheter system (Smiths medical, Grasbrunn, Germany) when possible. The probe was placed at the highest level of the subarachnoidal space (2 cm below the head’s highest point). In cases with compressed ventricular system a parenchymal probe was used instead (Codman ICP express®, Johnson & Johnson, Raynham, USA or Neurovent-PTO®, Raumedic AG, Münchberg, Germany).

Compliance (Paper IV-V)
Compliance was estimated by using the amplitudes in the ICP curve (126).

Cerebral blood flow pressure autoregulation - pressure reactivity index (Paper IV-V)
PRx is based on the correlation of ICP and MAP, so that when ICP is highly correlated with MAP, PRx approaches a maximum value of one. When MAP and ICP are uncorrelated or negatively correlated PRx tends to zero or negative values, with the minimum possible being minus one. Hence high values of PRx are associated with poor autoregulation, and low values with intact autoregulation (45).

Usually PRx is computed from the ICP and MAP waveforms by taking the average values of a series of 5 to 10-second segments over a duration of from 3 to 5 minutes. Then the correlation of the two series is computed to produce the index. Sometimes the waveforms are preprocessed using a bandpass filter to remove irrelevant low- and high-frequency variation (126, 169).

In the current studies we have used the methodology by Howells et al. (2014) (170). A filter with a bandpass of from 0.018 to 0.07 Hz was used. This means that the correlation analysis is limited to oscillations of MAP and ICP with periods of 15 to 55 seconds in duration.

Temperature (Paper V)
Temperature was monitored with a probe in the urinary bladder catheter (Mon-a-Therm™ Foley catheter with temperature sensor 400TM, Covidien, Regensburg, Germany).
Cerebral oxymetry (Paper V)

A Neurovent-PTO (Raumedic AG, Münchenberg, Germany) probe was used. The probe was routinely placed via a burr hole in the right frontal lobe. If a hemicraniectomy or evacuation of mass lesion was done on the left side the probe was placed in the left hemisphere.

Cerebral metabolism (Paper V)

The microdialysis catheter (71 High Cut-Off Brain Microdialysis Catheter® M Dialysis AB, Solna, Sweden) was placed close to the pressure device. The catheter was connected to a CMA 106 or 107 microinfusion pump® (M Dialysis AB). The perfusion fluid rate was 0.3 µL/min and the samples were collected every hour. Glucose, lactate, pyruvate and urea were analyzed using a bedside analyzer CMA 600® (CMA Microdialysis, Solna, Sweden). The L/P ratio was calculated. Quality control measurements, using control samples for CMA 600 MD Analyzer, were run daily. Total imprecision for all analyses had a coefficient of variation of < 10%. Probe performance was validated by monitoring interstitial fluid urea [30].

The Uppsala TBI register (Paper I)

All patients with TBI admitted to the NIC unit at Uppsala University Hospital are entered in the register. Data are extracted from the medical charts by a small group of persons. Predefined criteria are set up for the dataset. There are three columns for each patient where data are inserted. The first column includes admission data. The second column includes data from the NIC period about surgery, types of monitoring, if and how long the patient was intubated, complications and neurological condition at discharge. In this column it is also possible to register the extent of secondary insults as assessed from the monitoring. The third column is used for six months outcome follow-up.

Quality assurance components in The Uppsala TBI register

Automatic daily standardized summary reports on demand

Every day, on command, The Uppsala TBI register provides standardized summary reports on the webpage. Index of improvement is calculated as the difference between mean RLS at arrival and mean RLS at discharge. Index of change shows the difference between RLS at arrival and RLS at discharge and divides the patients in three groups: improved, unchanged and deteriorated. Talk and deteriorate report and Talk and die report show all patients
who have talked (RLS 1-2 on admission) and then deteriorated (RLS 3-8 at discharge) or died during NIC.

**Detailed analysis of database**

It is possible to export all data from all patients into a spreadsheet for detailed analysis and research. Every case has got one row and 114 columns. From this excel file it is possible to study for example the extent of secondary insults for every single patient.

**Specific reviews of compliance with standardized management protocols**

The occurrence of patients not responding to command who did not receive artificial ventilation and ICP monitoring, respectively, as prescribed in the standardized management protocol system, was investigated. A specific medical chart review was done for these cases to find explanations.

**Specific reviews of deteriorating cases**

A specific medical chart review was performed in cases with RLS 1-5 at arrival who deteriorated, to find reasons for their deterioration and to identify possible poor management.

**Outcome in The Uppsala TBI register**

The clinical outcome was assessed using GOSE (145) after 6 months (mean 8.2 months). In practice, specially trained nurses interviewed the patients by phone using a standard questionnaire (142). Children (≤ 15 years) were followed up by interviewing their parents or guardian after 6 months (mean 7.2 months) using the original GOS (141, 142).

**Bed-side computer-based secondary insult nurse checklist (Paper II)**

In this study, data from ICP, CPP, SBP and temperature from the first 7 days of monitoring were extracted. The extent of secondary insults was calculated as the proportion of GMT spent above/below defined insult levels for ICP, CPP and temperature.

The *feasibility* of using checklists was evaluated by counting to what extent the checklists were completed as prescribed by the standardized management guideline protocol.

The *accuracy* of using checklists was evaluated by comparing the checklist assessments with the actual occurrence of secondary insults according to the collected minute-by-minute monitoring data in four ways:

1. The proportions of *Yes* and *No* in assessed work shifts with no collected minute-by-minute values out of the treatment goal.
2. The duration in minutes spent at secondary insult level was compared between Yes and No assessments.
3. The numbers of Yes and No were analyzed in relation to the proportions of GMT spent above/below the defined insult level for all work shifts.
4. Sensitivity and specificity for the checklist assessments were calculated. A secondary insult was defined to have occurred if > 5% of GMT had been spent at insult level according to the collected minute-by-minute monitoring data.

Nursing interventions (Paper III-IV)

Definition of secondary insult related to nursing interventions (Paper III-IV)

In Paper III secondary insult had the definition of ICP > 20 mmHg, CPP < 60 mmHg or SBP < 100 mmHg for five minutes or more in a ten-minute period starting from when the nursing intervention begins. The insult minutes do not have to be consecutive (Figure 12). If a new intervention was started within five minutes of when the first intervention was initiated, the intervention was labelled as a simultaneous intervention because it was not possible to know which of the interventions influenced the patient.

In Paper IV we ensured that the patients were undisturbed for 30 minutes (pre-intervention periods A and B, both 15 minutes in duration) before the nursing intervention began. The mean baseline values of ICP, PRx and ICP amplitude were calculated for pre-intervention period B. The aim of pre-intervention period A was to avoid effects from previous interventions. A secondary ICP insult was defined as ICP ≥ 20 mmHg for five minutes or more during a continuous 10-minute interval. The entire insult had to occur within the intervention and postintervention A periods. It was necessary to include the postintervention A period because some interventions did not last for the 5 minutes required to fulfil the criteria for an insult (Figure 12). The observation was excluded if there was already an ongoing secondary insult when the nursing intervention began (Paper III-IV).
Performance of nursing interventions (Paper III-IV)

Oral care is done three times a day with a toothbrush after which foam swabs are used to cleanse the mouth of toothpaste. The patients are repositioned approximately every two hours as a routine and their heads are elevated 30° except for patients suffering from a SAH with clinical signs of vasospasm who lie flat. Endotracheal suction is only performed if necessary, on occasions with decreasing saturation, increasing peak pressure in the ventilator, coughing or sounds from the endotracheal tube. Strict hygiene, a negative pressure of 20 cm H₂O and as short procedures (10-15 s) as possible are prescribed in the standardized management protocol system (84). The patients are washed in bed with washcloths every morning and evening, and when needed.

Consequences of hyperthermia (Paper V)

In Paper V, the microdialysis pattern was classified in four categories for each patient, based on published normal and critical microdialysis levels [31-33]:

- Ischemia (L/P ratio > 40 and pyruvate < 50 µmol/L)
- Energy metabolic crisis (L/P ratio > 25 and pyruvate 50-120 µmol/L)
- Hyperglycolysis (L/P ratio < 40, lactate > 4 and pyruvate > 120 µmol/L)
The percentage of samples in each of the microdialysis categories was calculated for each patient. Furthermore, the MD samples were divided into high (38.0 – 42.0°C) and low (36.0 - 37.9°C) temperature groups in order to study the effects of temperature on cerebral metabolism.

Statistical methods (Paper I -V)

Paper I
Descriptive statistics were performed.

Paper II
T-tests were performed to detect differences between checklist assessment (Yes/No) of secondary insults and actual occurrence of secondary insults according to the minute-by-minute monitoring data. Statistical significance was set to p < 0.05. Furthermore, the sensitivity and specificity was calculated for the checklists. In the calculations of sensitivity and specificity, a secondary insult was considered to have occurred if > 5% of the GMT did not reach the treatment goals.

Paper III
Descriptive statistics were performed.

Paper IV
For comparing risk groups Chi-square test was used with p < 0.05 as level of significance. Risk ratio = insult rate with risk factor / insult rate without risk factor.

Paper V
Correlation analysis
When correlations are presented, the results are based on individual analysis of each patient. If the correlation coefficient (r) was > 0.3 it was defined as a positive correlation and if r was < -0.3 it was defined as a negative correlation. The median correlation coefficient (r) was calculated, as the median of all patients’ individual correlation coefficients. A positive median r for all patients indicates e.g. that higher temperature values are associated with higher ICP values. Correlation analysis was performed according to Pearson.
Comparison between groups
For comparing % of GMT with ICP > 20 mmHg in temperature groups (< or > than 39°C) and microdialysis values within microdialysis category, Wilcoxon Signed Rank Test was used. For comparing age and GCS-M, Mann-Whitney was used. Differences were considered to be statistically significant when p < 0.05.

Mixed models
In order to further explore the relationship between variables of interest, linear mixed models have been evaluated. In all models hyperthermia has been included as a fixed factor and patient as a random factor. To determine the effect of hyperthermia depending on different confounding factors, the first model for each factor included the interaction between hyperthermia and the factor of interest. In case of a nonsignificant interaction the interaction term was excluded from the model and the final model contained main effect for hyperthermia and the factor of interest. For all models the predicted values and 95% confidence intervals from the final model are presented in figures.

Ethical considerations
The patients were unconscious when they participated in the studies. Informed consent was obtained from their relatives. In Paper I, II and V no study interventions were performed. In Paper III and IV ordinary nursing interventions were observed and no extra interventions were performed. All studies were approved by the local ethics committee and the studies were performed according to the declaration of Helsinki (171).
RESULTS

Quality assurance by Uppsala TBI register (Paper I)

Automatic daily standardized summary reports

Index of improvement: The patients improved on average during the NIC stay (1.2 RLS levels in 2008, 0.7 RLS levels in 2009 and 0.9 RLS levels in 2010). Index of change: The proportion of patients improved in RLS scale during NIC varied between 80% in 2008 and 60% in 2009. Talk and die and Talk and deteriorate: The percentage of these patients was 0-1% (Figure 13).

![Image](image_url)

*Figure 13.* All 314 patients included in Uppsala TBI register during 2008-2010. Percent of patients talk (RLS 1-2 on admission) and die (dead during NIC), and talk and deteriorate (RLS 3-8 at discharge).

Detailed analysis of database

Admission to NIC unit

The mean GCS-M was $5.04 \pm 1.23$ (RLS $3.4 \pm 1.6$) at arrival to the NIC unit. The most frequent causes of injury were fall accidents (44%) and vehicle accidents (30%). The most common primary finding on the initial brain CT scan was contusions (33%) and acute subdural hematoma (23%).
Neurointensive care
The patients stayed at the NIC unit for 0-86 days (mean 11 ± 10 days). ICP was monitored in 54% of the cases and the duration varied between 1-50 days (mean 11.1 ± 7.3 days). Artificial ventilation was used in 75% of all cases between 0-46 days (mean 8.6 ± 7.6 days).

Occurrence of secondary insults
Analysis of the occurrence of secondary insults for all adult patients (≥ 16 years) according to predefined insult thresholds showed that ICP > 25 and > 35 mmHg, CPP < 50 and < 40 mmHg, SBP < 100 and < 90 mmHg, and MAP < 70 and > 120 mmHg occurred in less than 5% of GMT. CPP < 60, and SBP > 180 mmHg and MAP > 110 mmHg were present at an amount of 5-10% of GMT. CPP > 70, > 80 mmHg, SBP > 160 and MAP < 80 were present at more than 20% of GMT (Figure 14). Deteriorated patients had the same pattern of secondary insults (Figure 14).

Figure 14. Mean occurrence of secondary insults (% of GMT) according to predefined threshold levels in TBI patients with ICP monitoring ≥16 years (n=146) and in deteriorated patients ≥16 years (n=20), included in Uppsala TBI register during 2008-2010.
Neurological status at discharge
At discharge from the NIC unit, the mean GCS-M was 5.7 ± 0.8 (RLS 2.5 ± 2.0). The pupil reaction and size became more normal during the stay at NIC unit but the extent of paresis was almost the same at discharge (34%) as at arrival (36%).

Outcome
Of the adult patients (≥ 16 years) 41% had good recovery (GR), 23% moderate disability (MD), 19% severe disability (SD) and 1% (two patients) remained in a vegetative state (VS). Moreover 5% died at the NIC unit and 8% died within six months after discharge. Among the children (≤ 15 years), 61% showed GR, 15% MD, 9% SD. No child persisted in VS and 9% died at the NIC unit. Figure 15 shows the clinical outcome for all adult patients (≥ 16 years) based on the severity of the injury. The severity of injury was classified as mild, moderate and severe using the GCS-M score.

Figure 15. Six months outcome (GOS) divided by severity of injury at admission to the NIC unit in adult patients ≥ 16 years (n=181) included in the Uppsala TBI register during 2008-2010.
GR, good recovery; MD, moderate disability; SD, severe disability; VS, vegetative state; D, dead within 6 months; DM, data missing.
Specific medical chart review

Compliance with standardized management protocols
Among 173 cases who did not respond to commands (RLS 3b-8, GCS-M 1-5) at arrival to the NIC unit, ICP was not monitored in 36 (21%) cases. Explanations for not monitoring ICP were found in the medical records. Three cases who did not respond to commands (RLS 3b-8) at arrival to the NIC unit were not intubated and artificially ventilated. According to the medical records, the reason for not intubating those 3 cases was that they all made a very quick clinical improvement.

Deterioration in neurological status
Out of all patients that arrived in RLS 1-5 (n=282) to the NIC unit 20 patients deteriorated. Likely patient related explanations could be found in 19 cases (Table 5). No treatable children deteriorated. The three children who died arrived in RLS 8. Deteriorating patients had a similar extent of secondary insults compared with all patients (n=314) (Figure 14).

Table 5. Medical chart review – Possible patient related explanations and occurrence of patients in RLS 1-5 at arrival to the NIC unit who deteriorated among all 314 patients included in Uppsala TBI register during 2008-2010.

<table>
<thead>
<tr>
<th>Possible explanations</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old patient (&gt; 69 years)</td>
<td>1</td>
</tr>
<tr>
<td>Anticoagulantia or coagulopathy</td>
<td>1</td>
</tr>
<tr>
<td>RLS 4-5 at arrival</td>
<td>4</td>
</tr>
<tr>
<td>Two or more of the above mentioned explanations</td>
<td>11</td>
</tr>
<tr>
<td>Severe complication*</td>
<td>2</td>
</tr>
<tr>
<td>No explanations</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>

*Basilar dissection (n=1) and sinus thrombosis (n=1)

Evaluation of the bedside computer-based secondary insult nurse checklists (Paper II)
The study contained 546 work shifts where assessments on secondary insults (ICP, CPP, SBP, temperature) should have been conducted by nurses. The total number of assessments was 2184. The nurses documented their assessments in 84-85% of their shifts. High temperature was documented in 28% (155/546) of the shifts, high ICP in 13% (70/546), low CPP in 8% (41/546) and low SBP in 2% (13/546) of the shifts. Duration of monitoring time at insult level was significantly longer when Yes was filled in for ICP (mean
134 vs. 30 min), CPP (mean 125 vs. 26 min) and temperature (mean 315 vs. 120 min). For SBP, duration below threshold between Yes and No assessments did not differ significantly. When a secondary insult was defined to have occurred if > 5% of GMT was spent at insult level, the sensitivity was calculated to 31% for ICP, 38% for CPP and 66% for temperature. The specificity was 100% for ICP, 99% for CPP and 88% for temperature.

Secondary insults related to nursing interventions (Paper III-IV)

The total number of nursing interventions analyzed in Paper III was 1,717; oral care (n=171), repositioning (n=571), endotracheal suction (n=393), hygienic measures (n=93) and simultaneous interventions (n=489). The most common kind of secondary insults after a nursing intervention was high ICP (n=93) followed by low CPP (n=43) and low SBP (n=14). Repositioning (n=39) and simultaneous interventions (n=32) were the nursing interventions causing most secondary insults. There were substantial variations between the patients, where only one had no secondary insults. Three patients had secondary insults initiated by all kinds of nursing interventions (Figure 16). In a few occasions one nursing intervention caused more than one secondary insult at the same time. This occurred in 0-1.1% of the occasions.

Occasionally an ongoing secondary insult stopped after a nursing intervention. For example this occurred for high ICP at 17 times of 393 (4%) suctions and in 17 times of 571 (3%) after repositioning.
In Paper IV, 67 nursing interventions were done in the 28 patients. In 35 (52%) of these interventions ICP remained below 20 mmHg the entire time. A secondary ICP insult was observed in 6 (21%) patients and 8 (12%) occasions. Turning to lateral position was the intervention causing fewest secondary ICP insults (Figure 17).

Figure 16. Secondary insults on an individual basis. The x axes show patient numbers 1-18.
Predicting a secondary insult (Paper IV)

When using amplitudes (≥ or < 6 mmHg), baseline ICP (≥ or < 15 mmHg) and PRx (≥ or < 0.3) as predictors of risk of occurrence of secondary insult related to nursing intervention, baseline ICP showed the best combination of sensitivity (50%) and specificity (86%). Negative predictive value was high in all three groups and ICP ≥ 15mmHg had highest positive predictive value (33%).

The high risk cerebral autoregulation group had a risk ratio of 1.7 (i.e. 70% more insults than the low risk group), whereas the high risk intracranial compliance group had a risk ratio of 2.9 (190% more insults than the low risk group); these results were not statistically significant. The only statistically significant result was for the high risk ICP group, which had a risk ratio of 4.7, or 370% more insults than the low risk group (Table 6).

Table 6. Predicting secondary ICP insults related to nursing interventions using compliance, ICP and pressure autoregulation as predictive factors.

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Insult</th>
<th>No Insult</th>
<th>Risk ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude (≥ 6 mmHg)</td>
<td>5</td>
<td>20</td>
<td>2.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Amplitude (&lt; 6 mmHg)</td>
<td>3</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICP (≥ 15 mmHg)</td>
<td>4</td>
<td>8</td>
<td>4.7</td>
<td>0.01</td>
</tr>
<tr>
<td>ICP (&lt; 15 mmHg)</td>
<td>4</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRx (≥ 0.3)</td>
<td>3</td>
<td>15</td>
<td>1.7</td>
<td>0.47</td>
</tr>
<tr>
<td>PRx (&lt; 0.3)</td>
<td>5</td>
<td>44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Consequences of hyperthermia (Paper V)

In Paper V, 93 out of 103 (90%) patients had hyperthermia (> 38 °C) more than one hour during the first 10 days after start of monitoring. When analyzing the proportion of GMT for hyperthermia > 38°C by day, day seven showed the largest proportion of hyperthermia (Figure 18).

Figure 18. The occurrence of hyperthermia > 38°C (proportion of GMT) by day.

Hyperthermia and ICP

When all temperature and ICP values were plotted for each patient, patients with positive (r > 0.3): 14/87 (16%), negative (r < -0.3): 5/87 (6%) and patients without: 68/87 (78%) correlation between hyperthermia and ICP were observed.

When the occurrence of ICP insults (> 20mmHg) was compared between periods with temperature ≥ 39 °C and periods with temperature < 39 °C in individual patients (the 25 patients with time in both temperature ranges), there was significantly (p = 0.025) larger proportion of GMT with ICP > 20 mmHg in the higher temperature ranges. The median increase (difference in proportion of GMT with ICP > 20 mmHg) was 1% and 5 (20%) of the patients had increases over 25% (Figure 19).
Hyperthermia, intracranial compliance and ICP

The estimates of the mixed model including ICP, temperature and compliance are shown in Figure 20 with 95% confidence intervals. Seven temperature ranges were included with the highest being from 39 to 42 °C. In the group with poor compliance ICP increased about 2 mmHg, and was significantly increased in the highest temperature range compared to the four lowest ranges. In the group with good compliance the changes in ICP with increased temperature were not statistically significant.

Hyperthermia, pressure autoregulation and ICP

ICP was overall higher in the group with impaired pressure autoregulation (PRx > 0.3), and ICP also increased more with increasing temperature (Figure 20). In the impaired group mean ICP increased about 4 mmHg. The in-
crease was statistically significant when comparing the highest temperature range to any of the five lowest ranges, or comparing the second highest range with the four lowest. In the group with preserved pressure autoregulation the increase in ICP was about 3 mmHg, and the increase was significant only when comparing the highest range to the three lowest ranges (Figure 20).

*Figure 20.* Predicted values (and 95% CI) from a mixed model including ICP as dependent variable.
Hyperthermia and cerebral oximetry

Analysis of the relation between $B_{\text{tip}}O_2$ and hyperthermia showed both patients with positive correlation ($r > 0.3$): 3/16 (19%), no correlation 11/16 (68%) and negative correlation ($r < -0.3$): 2/16 (13%).

A mixed model including temperature and $B_{\text{tip}}O_2$ (dependent variable) showed that $B_{\text{tip}}O_2$ increased when temperature increased, although the changes were not statistically significant. The relationship between $B_{\text{tip}}O_2$ and temperature was not influenced by ICP (Figure 21).

Figure 21. Predicted values (and 95% CI) from a mixed model including $B_{\text{tip}}O_2$ as dependent variable and temperature as independent variables.

Hyperthermia and cerebral metabolism

The overall result for all energy metabolic microdialysis substances in individuals showed that no correlation ($r = 0.3 - -0.3$) with temperature was the most common finding followed by positive correlations ($r > 0.3$) and negative correlations ($r < -0.3$) (Figure 22).
A mixed model (compensating for ICP) including temperature and all energy metabolic microdialysis substances (dependent variables) were made (Figure 23). Temperature did not influence glucose or L/P ratio. Lactate and pyruvate increased when temperature increased, although the changes were not statistically significant (Figure 23).
Figure 23. Predicted values (and 95% CI) from mixed models including energy metabolic microdialysis substances (glucose, lactate, pyruvate and L/P ratio) as dependent variables and temperature as independent variable.

The hourly microdialysis sample for each patient (n=28) was categorized into the metabolic patterns. Ischemia was never observed, energy metabolic crisis was observed in 11% (271/2555) of the samples, hyperglycolysis in 34% (862/2555) and normal energy metabolism in 55% (1422/2555). The relative occurrence (proportions of samples) in individual patients of each microdialysis category by temperature showed no significant differences in the occurrence of MD categories depending on whether the patients had temperature 36°C–38°C or 38°C–42°C when the microdialysis sample was collected.
DISCUSSION

In the work with this thesis, the established standardized management protocol system based on GLP principles, and the multimodality monitoring, computerized data collection and analysis systems constituted a valuable platform for the research (9, 172). It was also obvious that this approach was valuable for the care of the patients according to the extent of secondary insults found and the clinical outcome observed. Since all staff members are involved in the development and maintenance of the standardized management protocol system, the general knowledge among the staff is increased and the staff members become more motivated to follow the protocol. Thus, the patients are cared for and treated in a better and more uniform way. In order to find ways of increasing the quality of NIC further, different approaches were used in the studies of this thesis, which are reviewed and discussed in the following sections.

Quality assurance by the Uppsala TBI register (Paper I)

The main goal of establishing the Uppsala TBI register was to obtain an instrument for regular quality assurance of the management of TBI with particular focus on the NIC period. Therefore, a battery of quality assurance components suitable for NIC was introduced to reflect the quality of NIC in different aspects.

Automatic daily standardized summary reports on demand

The idea with the standardized summary reports was to be able to get updated reports on demand, with predefined selections of patients for overview and comparison. For example the proportion of patients improved in RLS scale during NIC varied between 80% in 2008 and 60% in 2009. In 2009 exceptionally many TBI patients arrived in GCS-M 6 and 1, and they were often unlikely to improve. The extent of deteriorated patients was stable and less than 10% during the period. The reports should include traditional demographic data, crude outcome data and outcome in relation to established prognostic admission factors. Furthermore, new quality measures were included in the reports with inspiration from the description of patients with head injuries who talked and died due to secondary brain injury in the 1970s.
in Glasgow (4) i.e. occurrence of talk and die cases, and occurrence of talk and deteriorate cases. In this material, < 1% of the TBI patients talked and died whereas about 6% have been reported by others (149, 173). Talk and deteriorate cases, which means patients who are awake on admission and then deteriorate (167), were also rare and occurred in fewer than 1% of the patients.

Our impression is that the standardized summary reports on demand provide a valuable tool to monitor demographic changes over time and the quality of care in TBI patients. The possibility of getting updated reports on demand every day is a great advantage. Inclusion of the different quality measures developed from the talk and die concept adds valuable information to ordinary long-term outcome analysis by reflecting the NIC period specifically. These measures need to be evaluated further.

**Review of deteriorating cases**

In order to better understand why some patients (both initially conscious and unconscious) deteriorated during their stay at the NIC unit and to identify suboptimal care, we did a specific medical chart review of all patients who were RLS 1-5 on admission and then deteriorated or died. In this series of patients, the specific medical chart review found that 17 out of 20 deteriorating patients had patient related factors (i.e. high age, ongoing anticoagulation treatment or coagulopathy, severe neurological status at arrival) contributing to the deterioration. Two patients had complications (basilar dissection, n=1, sinus thrombosis, n=1) which were judged not to have been preventable. Only one patient had no obvious reason for deterioration and he deteriorated from RLS 3b to RLS 4. This structured way to investigate patients who deteriorate during the stay at NIC unit illustrates a way to survey the occurrence of avoidable factors contributing to poor outcome, e.g. misjudgments, mis-treatments and complications that can be avoided.

**Reviews of compliance with standardized management protocols**

It is well established that application of management protocols improves care (9, 165). However, the compliance with management protocols has been found to be as low as about 50 % (174, 175). In this study, we checked for the compliance with two crucial standardized management principles, i.e. ICP monitoring and artificial ventilation. The compliance with the indication for ICP monitoring was 79% and for artificial ventilation 98%. When the reasons were investigated for not monitoring ICP when indicated according to the management protocol, reasonable explanations were found, e.g. coagulopathy. It is important according to our opinion that quality assurance programs include evaluation of compliance with applied management protocols and reasons for exclusions.
Detailed analysis of database

**Admission to neurointensive care unit**

Patients of all ages were admitted to the NIC unit and all ages are represented in the material with two peaks at about 20 and 60 years. The percentage of patients who were in the mild coma grades on admission (RLS 1-3a/GCS-M 6) was 44% compared to only 10% in the severe grades (RLS 6-8/GCS-M 1-3). Falls (44%) and vehicle (30%) accidents were the most common causes of TBI, which is rather similar to studies from Finland (27) but different from some other countries (149, 150, 152). Regular evaluation of the automatic summary reports on demand in combination with the detailed analysis of the database can be used to follow any changes in demographic patterns over time for TBI.

**Neurointensive care period**

It is difficult to compare the duration of stay at the NIC unit between different centers due to different structure and organization of the health care. Analysis of the TBI cases managed in Uppsala revealed that duration of stay varied considerably (0-86 days) but was about 11 days on average. Another study from Austria reported a mean of 10 days at intensive care unit for TBI patients (176).

It was also interesting to observe that intracranial hematomas/contusions were evacuated in 30% of all cases and that barbiturate coma treatment and decompressive craniectomy was required in 8% and 6% of the patients, respectively, which underlines the need for highly specialized care of TBI.

**Occurrence of secondary insults**

To our knowledge, quantification of secondary insults during NIC has never been mandatory in any quality assurance program for TBI management, although specific studies of secondary insults have been performed (177-180). No ideal quantitative measure of secondary insult burden exists. We believe that a proportion of GMT above/below a defined threshold level for certain types of insults provides accurate information (167, 178). Quantification of secondary insults within this quality assurance program showed that all investigated parameters except four had less than 10% of GMT out of the threshold; ICP > 25 mmHg occurred in 4.5% of GMT and SBP < 100 mmHg in 1.7% of GMT. Thus, the occurrence of secondary insults appears to be low. Quantification of secondary insults during NIC is of utmost importance in any quality assurance program concerning TBI management.
Clinical outcome
The Uppsala TBI register includes all patients managed at the NIC unit without selections, which is preferable when the overall results are reported and for comparisons. It is also important that the clinical outcome is assessed in an established and validated way. The GOS, both original form and extended version, is assessed reliably by a structured interview and the result describes an overall social outcome (141). Looking at the follow-up results of this patient material, 64% of the adult patients had a favorable outcome (GR or MD). This result can be compared with other studies which reported favorable outcome in 50-70% of the cases (181-185) and the earlier results from Uppsala presented by Elf et al. (2002) who reported favorable outcome in 78% of the cases treated during 1996-1997 (9). Stein et al. (2010) show in a systematic review that the improvement in mortality had not continued after 1990 (186). It should be emphasized that it is difficult to compare overall results between different studies because of differences in e.g. the selection of patients and demographics. The TBI patients treated in Uppsala 1996-1997 were younger but in poorer GCS-M grade at admission compared to the present series and patients potentially not possible to treat were excluded (n=18) (9). The results from the present study also showed that younger patients and patients with better neurological status at arrival had better outcomes overall which is in accordance with other studies (98, 135). The children in our material made a GR in 61% of the cases and 9% died at the NIC unit, which is comparable with another Swedish study (187).

Bedside computer-based secondary insult nurse checklists (Paper II)
The NIC nurse was identified as the key person responsible for reducing the occurrence of secondary insults (11, 76). The nurse checklist for documentation of the occurrence of secondary insults were introduced as part of a secondary insult program initiated at our NIC unit with the hope that maximal attention should be paid on avoiding secondary insults and that the checklists should facilitate quick evaluation of the patients. The working conditions in critical care are usually intensive and mainly focused on life-saving procedures and, even if important, documentation is a secondary task. The principles for routine documentation need to be straight and simple to be useful. The finding that the nurses conducted their documentation in as much as 85% of the occasions during NIC conditions indicates that a computer-based checklist was feasible in the NIC.

The mean duration of insults from the collected monitoring data showed a statistically significant difference between Yes and No for ICP, CPP and temperature. It is apparent in this analysis that the checklist assessments
were relatively accurate. It should also be emphasized that it was not possible to define exactly in the standardized instruction when insults should be assessed to have occurred during a shift since the patterns may look very different, e.g. high values during a very short continuous period of time, values close to goal during a long continuous period of time, or scattered values at insult level. Instead, the overall impression of whether the patient reached the treatment goals or not according to the nurse’s clinical experience was applied.

For the specificity and sensitivity calculations, 5% of GMT spent at insult level was used as a cut-off to decide whether a secondary insult had taken place. The result shows that there is a good specificity and a poor sensitivity for the checklist assessment of secondary insults, i.e. high probability of No if secondary insults had not occurred and low probability of Yes if secondary insults had occurred. In other words, by using the assessment it is easier to correctly identify a true absence of secondary insults than to correctly identify a true presence of secondary insults. A cut-off of 5% is low and taking into consideration that many insult values may also be close to the insult threshold and scattered over time, this result indicates that the assessment is clinically relevant. One explanation for the low sensitivity could be that the nurses do not feel concerned about secondary insults if they know the reason or if the insult occurs in many short periods that altogether make a high percentage of GMT.

A subjective impression was clearly that the checklists positively influenced the management of the patients and facilitated the evaluation of the patients.

Checklists could be used in other fields to detect and highlight risk factors important for that particular group of patients.

Secondary insults related to nursing interventions (Paper III-IV)

Although the extent of secondary insults related to nursing interventions was low in general, some patients were afflicted with numerous occasions of secondary insults during the stay at the NIC. It is important to recognize the patients who have an increased risk of secondary insults and then perform and plan their care and treatment in a more individualized way.

Paper III is the first study to investigate the extent of secondary insults caused by nursing interventions using defined criteria for when a secondary insult has occurred.

In this study repositioning resulted in the highest extent of secondary insults which was also the result in the study by Tume et al. (2011) in pediatric patients (80). Oral care did not influence ICP in this study, similar to the
study by Prendergast (77). Some patients in the present study had secondary insults in one-third of nursing interventions and other patients had none. This suggests that some patients are more prone to develop secondary insults after nursing interventions.

A common way to perform nursing interventions at a NIC unit is to do additional interventions at the same time in order to not disturb the patient too often. In this study simultaneous interventions were analyzed and for some individuals it appeared to be better to perform one intervention and let the patient stabilize before performing the next. If nursing interventions are made simultaneously the procedure will also take longer time and the patient may stay at insult level for a longer time.

The worst kind of secondary insults is when more than one treatment goal is not achieved, which was very rare in this material.

This study concluded that secondary insults induced by nursing intervention were relatively sparse and that there was considerable patient variation.

This result raised the question if it was possible to identify the risk patients before the nursing intervention was started. A new study (Paper IV) was organized with the aim to further study the risk of inducing high ICP in relation to nursing interventions and to evaluate whether ICP amplitudes, baseline ICP level or PRx could be used to identify risk patients.

In Paper IV, secondary ICP insults occurred in 12% of the nursing interventions compared to 5% in Paper III. A possible reason may be that in Paper III it was allowed to open the ventricular drainage after intervention if ICP tended to be high in some patients.

Concerning the methodology in Paper III and IV, the inclusion of data was well controlled and all interventions were made in a standardized way. The fact that the author (LN) attended during all occasions in Paper IV when data were collected may have influenced the results. When studying processes in a NIC unit it is difficult to avoid confounders. However, a relatively large number of nursing interventions were investigated.

The definition of when a secondary insult had occurred must be considered. The five-minute duration was chosen as a minimum duration by which it is reasonable to believe that a secondary insult may harm the brain. In our study it was necessary to detect insults within a very restricted time frame, and we did not want to exclude cases where there were five full minutes over insult threshold, separated by only brief intervening periods below threshold.

Predicting the risk of secondary insult in association to nursing intervention (Paper IV)

The proportion of nursing interventions causing a secondary insult with ICP > 20 mmHg for five minutes or more was 12%. All these secondary insults occurred in 6 out of 28 patients. This indicates that relatively few patients
have an increased risk of secondary ICP insults in association with nursing interventions. The main result of the study was a significant difference in occurrence of insults between the groups with high and low baseline ICP. It was easier to identify patients with low risk for secondary ICP insults related to nursing interventions than the patients with high risk, i.e. the specificity was high and the sensitivity was low.

Theoretically, patients with exhausted adaptive capacity (high amplitudes) should have an increased risk of developing secondary ICP insults when a nursing intervention is performed. Furthermore, patients with disturbed pressure autoregulation should also have an increased risk of developing high ICP if a nursing intervention gives stress that increases the blood pressure. Although the results regarding the parameters relating to intracranial compliance (ICP amplitude) and cerebral autoregulation (PRx) were not statistically significant, it should be noted that patients classified as having poor compliance (ICP amplitude ≥ 6 mmHg) had ICP insults at a rate 2.9 times that of patients with good compliance, whereas patients with poor autoregulation (PRx ≥ 0.3) had insults at a rate 1.7 times that of patients with good autoregulation.

Finally, there was a significant difference in occurrence of insults between the groups with high (≥ 15 mmHg) and low (< 15 mmHg) baseline ICP. This could contribute to a better understanding on how to identify patients at risk for secondary insults caused by nursing interventions.

A decision-making tool for nursing interventions (Paper IV)

Nurses at a NIC unit continuously take decisions about which nursing interventions should be performed. They have to consider both the positive effects that the intervention could have for the patient and the risk that the patient develops a secondary insult related to the nursing intervention. A clinical tool to predict each patient’s risk for developing a secondary insult related to a nursing intervention could be helpful in daily practice. A decision-making tool for planning nursing interventions was designed based on the results of Paper IV (Figure 24). If the patient’s ICP is less than 15 mmHg all nursing interventions should be performed to prevent possible future secondary insults. It should be ensured that the patient is comfortable during the intervention. For patients with ICP 15-20 mmHg, nursing interventions should be performed in a way that minimizes the probability of secondary insults. Only the most important interventions should be chosen. The intervention should be well planned. For example, care should be taken to correct the body position for optimal venous outflow. Extra sedation/pain relief should be considered. When ICP is > 20 mmHg only nursing interventions intending to stop an ongoing secondary insult should be performed, e.g. suction in endotracheal tube. Extra sedation and pain relief should be given. In some occasions a nursing intervention has to be done no matter what. If that
kind of occasion occurs with a patient at risk for developing a secondary insult, the intervention should be done with considerable care for example with qualified personnel and extra sedation, pain relief and necessary equipment nearby.

Nursing interventions

<table>
<thead>
<tr>
<th>Baseline ICP</th>
<th>ICP &lt; 15 mmHg</th>
<th>Aim</th>
<th>To prevent possible future secondary insults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure</td>
<td>Ensure that the patient is comfortable during the intervention.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline ICP</th>
<th>ICP 15-20 mmHg</th>
<th>Aim</th>
<th>To prevent impending secondary insults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure</td>
<td>Plan the intervention well and choose the most necessary interventions. Give extra sedation and pain relief before, if needed.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline ICP</th>
<th>ICP &gt; 20 mmHg</th>
<th>Aim</th>
<th>To stop ongoing secondary insults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure</td>
<td>Perform a minimum of well planned nursing interventions. Give extra sedation and pain relief some minutes before the intervention.</td>
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<td></td>
</tr>
</tbody>
</table>

Figure 24. Decision-making tool for nursing interventions in the NIC.

Consequences of hyperthermia (Paper V)

Hyperthermia is a frequent secondary insult in the NIC which deserves further studying in order to improve temperature treatment (89-94). When studying the effects of hyperthermia on ICP in TBI patients it is important to take into account the complexity of the intracranial dynamics (34) including factors such as pressure-volume relationship and intracranial compliance, and pressure autoregulation of CBF. Furthermore, it is of interest to analyze the effects of hyperthermia on cerebral metabolism per se because of the metabolic regulation of CBF, which also may influence the hyperthermia effect on ICP. Theoretically, it is also of interest to study the brain oximetry since it is reasonable to believe that hyperthermia should influence \( B_{tp}O_2 \) by increasing the metabolism and consumption of oxygen as well as the delivery of oxygen due to the flow metabolism coupling.

Our hypothesis was that hyperthermia would raise cerebral energy metabolism. CBF increases to meet the increased energy demand. ICP may also
increase because of the increased cerebral blood volume (CBV). Furthermore, stress may also increase CBF, CBV and finally ICP. The changes in \( B_{\text{nPO}_2} \) and MD glucose depend on the balance between energy delivery and consumption. The ICP increase may also be dependent on compliance and pressure autoregulation (Figure 25).

![Diagram](image.png)

*Figure 25. The hypothesis on how hyperthermia would increase ICP.*

**Hyperthermia and ICP, ICP amplitude and pressure reactivity index**

To address the question whether hyperthermia caused clinically significant increases in ICP we compared the occurrence of ICP insult (≥ 20 mmHg) during periods of high temperature (≥ 39°C) with periods of low temperature (< 39°C). The result demonstrates that high temperature was associated with increased risk of ICP insults. For most patients however, the increased risk was negligible, since the median increase (difference in proportion of GMT with ICP > 20 mmHg) was only 1%. On the other hand the increased risk of secondary ICP insults was of potential clinical significance in several cases; 5/25 (20%) of the patients had increases over 25% (Figure 19).

Patients with low compliance and/or impaired pressure autoregulation had a higher increase in ICP when hyperthermia occurred. This could be explained by the fact that these patients are more sensitive for raised CBF/CBV.

**Hyperthermia, cerebral oximetry and metabolism**

The overall picture found in the mixed model analysis was that \( B_{\text{nPO}_2} \) increased with increasing temperature. This result is the same as in one other previous study (188). The increase of \( B_{\text{nPO}_2} \) is probably an effect of both preserved coupling between metabolism and flow and increased CBF due to stress, especially if pressure autoregulation is impaired. The results may also have been influenced by the Hb-O\(_2\) dissociation temperature dependency (54).

The mixed linear model showed a slight increase of both pyruvate and lactate by increasing temperature (statistically not significant), whereas the L/P ratio and glucose were relatively stable. This finding may indicate that
the occurrence of hyperglycolysis is higher during hyperthermia. When the defined microdialysis categories were studied, ischemia was never found but energy metabolic patterns indicating normal metabolism, nonischemic energy metabolic crisis and hyperglycolysis were seen. Normal energy metabolism and hyperglycolysis were most common and nonischemic energy metabolic crisis was rare. The occurrences of these defined patterns were similar in both temperature groups.

General considerations

The fact that all patients in the study were treated with the goal that temperature should be $< 38 \, ^\circ C$ and ICP $< 20 \, \text{mmHg}$ could have influenced the result. The result may possibly have been different if hyperthermia and ICP had been untreated. There are also several other methodological problems, which are difficult to overcome. One problem is that ICP and temperature have different temporal characteristics, i.e. ICP can change very quickly while temperature changes slowly. Another methodological problem is that ICP may increase for many different reasons in addition to hyperthermia, i.e. that the ICP level is fluctuating for many reasons that are not depending on temperature. These problems may also partly explain inconsistent results between different studies (92, 189-192).

Finally, it is of great interest to discuss if and when hyperthermia should be treated bearing in mind that the effects of hyperthermia on ICP, brain energy metabolism and $B_t\text{pO}_2$ differed considerably in this study, which indicates that hyperthermia may not always be hazardous. It is also difficult to treat hyperthermia and there are side-effects of the treatment. One side-effect of hyperthermia reduction is shivering (95, 97). Hata et al. (2008) have studied changes in systemic oxygen consumption in TBI patients treated with surface-cooling device to achieve normothermia (101). The patients who developed shivering had no significant reduction in systemic oxygen consumption after temperature reduction. The patients who did not develop shivering had significant improvement in systemic oxygen consumption (101). In a study with 15 patients, shivering significantly decreased the $B_t\text{pO}_2$ and the magnitude of shivering was associated with the degree of decreased $B_t\text{pO}_2$ (102). Patients treated with surface-cooling device have to be deeply sedated and this increases the risk for low blood pressure and the sedation also obstructs NWT. Pharmacological interventions to reduce hyperthermia are common. Paracetamol is often used but it can be associated with hepatic toxicity as a side-effect. Treating hyperthermia may also hide the symptoms of an infection and therefore delay treatment of infections (95). One way to identify which patient would benefit from reducing hyperthermia is to use multimodality monitoring devices. If a TBI patient with hyperthermia has problems with ICP, $B_t\text{pO}_2$ or cerebral energy metabolism, hyperthermia should be treated. Further studies are needed on this topic to
obtain better guidelines when hyperthermia should be treated in order to get a more individualized approach, which the results of this study illustrate the need for.
CONCLUSIONS

• The Uppsala-TBI register enables the routine monitoring of NIC quality indexes. If quality is measured routinely, problem areas can be identified and corrected continuously, which should produce improvements in NIC and outcome for TBI patients.

• Computerized secondary insult nurse checklists were feasible and appeared relatively accurate. Checklists may increase the alertness for avoiding secondary insults and help the evaluation of the patients. This concept may be the next step towards tomorrow’s critical care.

• Secondary brain insults occurred in about 10% of the nursing interventions. There were substantial variations in the extent of secondary insults related to nursing interventions between patients. The risk ratios of developing an ICP insult were 4.7 when baseline ICP ≥ 15 mmHg, 2.9 when ICP amplitude ≥ 6 mmHg and 1.7 when pressure autoregulation ≥ 0.3. Secondary ICP insults related to nursing interventions may be reduced by using a decision-making tool based on baseline ICP.

• The effects of hyperthermia on ICP were not extensive in general but there was an individual variation. Compliance and PRx influenced the ICP reaction but to a small extent. Microdialysis never showed ischemia and BtipO₂ tended to increase with increased temperature. From these results it appears that hyperthermia may not always be hazardous.

• Treatment of hyperthermia has many side-effects. It is desirable to gain more knowledge about which hyperthermia episodes are hazardous and should be treated. Information from the multimodality monitoring devices may be used to guide treatment. Hyperthermia should be treated if a TBI patient with hyperthermia has problems with ICP, BtipO₂ or cerebral energy metabolism.
SUMMARY IN SWEDISH - SVENSK SAMMANFATTNING

Bakgrund
Det har varit känt sedan 1970-talet att förekomst av så kallade sekundära insulter (t.ex. hypotension, hypoxi och högt intrakraniellt tryck) efter en traumatisk hjärnskada (THS) försämrar patientens utfall. Sedan dess har flera studier av patienter med THS visat vikten av att undvika alla typer av sekundära insulter under alla skeden av vården. Insikten om hjärnans vulnerabilitet efter en primär hjärnskada och vikten av att undvika sekundära insulter har implementerats i neurointensivvården för alla typer av neurokirurgiska patienter vilket lett till stora förbättringar avseende mortalitet och morbiditet. Samtidigt har den prekliniska forskningen utvecklat potentiella neuroprotektiva läkemedel men ett stort antal randomiserade studier har inte kunnat påvisa någon positiv effekt på människa.

Att vårda patienter med akut hjärnskada är komplext och kräver ständig monitorering. Sekundära insulter ska inte bara identifieras, de måste framför allt förebyggas och behandlas. Det är mot denna bakgrund angeläget att fortsätta utveckla vården och omvårdnaden i syfte att reducera förekomsten av sekundära insulter och sekundär hjärnskada ytterligare.

Övergripande syfte
Det övergripande syftet var att utveckla strategier för att minimera antalet sekundära insulter vilket kan leda till färre sekundära hjärnskador hos patienter med akut hjärnskada inom neurointensivvården.

Delarbeten
Introduction of the Uppsala Traumatic Brain Injury register for regular surveillance of patient characteristics and neurointensive care management including secondary insult quantification and clinical outcome
Uppsala TBI register startades med syftet att göra fortlöpande utvärderingar av verksamhetens kvalitet. Registret är konstruerat både för att göra automatiska rapporter och för att kunna sammanställa mer detaljerade data. En

The use of nurse checklists in a bedside computer-based information system to focus on avoiding secondary insults in neurointensive care

Att använda en checklista för att dokumentera sekundära insulter håller uppmärksamheten skäpt i arbetet att upptäcka och behandla sekundära insulter och förenklar överblicken av patienterna. För att förenkla registreringen av sekundära insulter som inte givit vika på sedvanlig behandling inrättades en checklista för sjuksköterskor att fylla i efter varje arbetspass. Checklistan besvarades genom att dokumentera ja eller nej på om det funnits problem med sekundära insulter. Checklistans användarvänlighet och hur väl dess dokumentation överensstämde med monitordata studerades. Av de 2184 arbetspass som studerades var 85 % ifyllda vilket visade på tillfredsställande användarvänlighet. Vid de tillfällen där det fanns dokumenterat att det förekommit sekundära insulter visade monitordata signifikant fler minuter med intrakraniellt tryck (ICP) > 20mmHg (i medeltal 134 vs. 30 minuter), cerebralt genomblödningstryck (CPP) < 60mmHg (i medeltal 125 vs. 26 minuter) och temperatur > 38oC (i medeltal 315 vs. 120 minuter). Specificitets- och sensitivitetsberäkningar visade att checklistans specificitet var 31-66 % och dess sensitivitet var 88-100 % för de olika typerna av sekundära insulter.

Secondary insults related to nursing interventions in neurointensive care: a descriptive pilot study

Omvårdnadsåtgärder görs regelbundet dygnet runt på neurokirurgiskapatienter som vårdas på en neurointensivvårdsavdelning. Syftet med den här studien var att studera hur ofta omvårdnadsåtgärder ledde till en sekundär insult. En sekundär insult definierades som ICP > 20mmHg, CPP < 60mmHg och systoliskt blodtryck < 100mmHg under minst 5 minuter under en 10-minuters period med start då omvårdnadsåtgärden påbörjades. Tjugonio patienter inkluderades och 1717 omvårdnadsåtgärder studerades. Den vanligaste sekundära insulten var ICP > 20 mmHg och det förekom vid 5 % av omvårdnadstillfällena. De omvårdnadsåtgärder som förorsakade flest sekundära insulter var vändningar och när flera omvårdnadsåtgärder gjordes i en följd. Generellt resulterade omvårdnadsåtgärder sällan i sekundära insulter men några patienter drabbades flera gånger. Patienter som löper ökad risk att drabbas måste identifieras och deras omvårdnad måste planeras och genomföras med stor noggrannhet.

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A decision-making tool to prevent secondary ICP-insults related to nursing interventions – Evaluation of the predictive value for baseline ICP, compliance and autoregulation

Som en fortsättning på föregående arbete var syftet i denna studie att undersöka om intrakraniell compliance, ICP i vila eller autoregulation mätt som PRx kunde förutsäga vilka patienter som riskerade att utveckla sekundära insulter i samband med omvårdnadsåtgärder. Tjugoåtta patienter med THS inkluderades. Fyrtionio stycken vändningar och 18 stycken hygienåtgärder observerades. Hypotesen var att patienter med ICP amplituder > 6 mmHg, ICP > 15 mmHg och PRx > 0,3 före omvårdnadsåtgärden skulle löpa större risk att utveckla en sekundär ICP insult (ICP ≥ 20 mmHg minst 5 minuter under en 10-minuters period) i samband med åtgärden. Insulter inträffade hos 6 av 28 patienter och vid 12 % av tillfällena. ICP > 15 mmHg före åtgärden var den prediktor som bäst kunde förutse vilka patienter som riskerade att drabbas av insulter. Ett sätt att undvika sekundära insulter i samband med omvårdnadsåtgärder skulle kunna vara att använda verktyg baserat på ICP i vila för att avgöra när olika typer av omvårdnadsåtgärder är lämpliga.

The effects of hyperthermia on intracranial pressure, cerebral oxymetry, and cerebral metabolism in traumatic brain injury patients during neurointensive care

Hypertermi är vanligt förekommande hos patienter med THS och det betecknas som en sekundär insult. Syftet med den här studien var att studera sambandet mellan ICP och kroppstemperatur samt att undersöka om compliance eller autoregulationen av blodflödet till hjärnan påverkade det förhållandet. Även hjärnans syrgastryck (BtipO2) och energimetabolism i relation till kroppstemperatur studerades. I studien inkluderades 103 patienter i åldrarna 15-80 år (median 41.0 IQR 34). 90 % av patienterna hade hypertermi (> 38°C) minst en timme under de första 10 dagarna. Generellt påverkade hypertermi inte ICP till en kliniskt signifikant grad. Patienter med låg compliance och/eller störd autoregulation påverkades något mer. Hypertermi påverkade heller inte BtipO2 eller hjärnans energimetabolism i någon större utsträckning hos majoriteten av patienterna. Microdialysen visade aldrig ischemi. Multimodal monitorering kan vara ett sätt att hitta de patienter som kan gynnas av febersänkande behandling.

Konklusion

Med ett kvalitetsregister (Uppsala TBI-register) kunde insultbördan samt flera andra kvalitetsindikatorer hos patienterna med THS kartläggas. Genom att regelbundet kunna följa kvaliteten på vården kan förbättringar göras fortlöpende. Med hjälp av en checklista kunde sjuksköterskorna identifiera pati-
enter med många sekundära insulter i relativt stor utsträckning. I checklistan var feber den mest förekommande sekundära insulten. Cirka 10 % av de studerade omvårdnadsåtgärderna resulterade i en sekundär insult. ICP > 15mmHg i vila var den bästa prediktorn för att hitta patienter som löper ökad risk att drabbas av en sekundär insult i samband med en omvårdnadsåtgärd. Hur hypertermi påverkar intrakraniell dynamik är olika för olika individer. Patienter med störd autoregulation av hjärnans blodflöde och patienter med låg compliance drabbades av ökat ICP i större utsträckning än andra patienter. Multimodal monitorering kan troligen visa vilka patienter som inte påverkas intrakraniellt av hypertermi och vilka patienter som behöver behandling mot hypertermi. Sammanfattningsvis kan konstateras att patienterna generellt sett drabbas av få sekundära insulter i de studier som gjorts.

Projektets betydelse
Genom att på olika sätt förbättra alla moment i neurointensivvården för patienter med akut hjärnskada kan mortalitet och morbiditet ytterligare förbättras. Resultatet av detta avhandlingsarbete kan leda till säkrare omvårdnadsåtgärder med mindre risk för sekundära insulter, fördjupad förståelse för hur hypertermi påverkar patienter med THS samt kunskap om hur Uppsala TBI-register och checklistan kan underlätta kvalitetsuppföljningar.
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REFERENCES

30. Kellie G. An account of the appearances observed in the dissection of two of three individuals presumed to have perished in the storm of the third and whose bodies were discovered in the vicinity of Leith on the morning of the 4th, November 1821, with some reflections on pathology of the brain. Transactions of the Medico-Chirurgical Society of Edinburgh. 1824;1:84-169.
85. Costello LA, Lithander FE, Gruen RL, Williams LT. Nutrition therapy in the optimisation of health outcomes in adult patients with moderate to severe


101. Hata JS, Shelsky CR, Hindman BJ, Smith TC, Simmons JS, Todd MM. A prospective, observational clinical trial of fever reduction to reduce systemic


119. Presciutti M, Schmidt JM, Alexander S. Neuromonitoring in intensive care: focus on microdialysis and its nursing implications. The Journal of


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