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Kari Schirmer-Mikalsen

Traumatic brain injury: control of physiological variables, organ failure and complications in the intensive care unit

NTNU
Norwegian University of
Science and Technology

Doctoral thesis

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Thesis for the Degree of
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Table of contents

Table of contents 1
Acknowledgements 3
List of papers 5
Acronyms 7
Sammendrag 9
Summary 11
1. Introduction to study 13
1.1 Focus / topic 13
1.2 Perspective / Rationale 14
1.3 Review of research 17
1.3.1 Diagnosing the TBI 17
1.3.2 The TBI guidelines 18
1.3.3 ICU treatment of TBI patients 22
1.3.4 Deviations from treatment protocols 35
1.3.5 Extracranial complications 36
1.3.6 Mechanical ventilation in patients with TBI 40
1.3.7 St. Olav's University Hospital 42
2. Aims of study 45
2.1 Study 1 45
2.2 Study 2 45
2.3 Study 3 45
3. Materials and Methods 47
3.1 Patients and setting 47
3.2 TBI treatment and treatment goals during the study periods 48
3.2.1 Study 1 and 2 50
3.3 Study 3 (2013-2014) 53
3.4 Outcome variables 55
3.5 Statistics 56
3.6 Ethical considerations 57
4. Results – Summary of papers 59
4.1 Study 1 – Paper I 59
4.2 Study 2 – Paper II 63

4.3 Study 3 - Paper III 67
5. Discussion 71
5.1 The importance of a TBI treatment protocol 71
5.2 Study 1 and Study 2 74
5.2.1 ICP and CPP 74
5.2.2 ICU treatment of TBI patients 76
5.2.3 Extracranial complications 81
5.3 Study 3 85
5.3.1 Mechanical ventilation in patients with TBI 85
5.3.2 PC versus PRVC ventilation 86
5.4 Methodological considerations 88
5.4.1 Single center studies versus multicenter studies 88
5.4.2 Observational studies 88
5.4.3 Randomized controlled studies (RCTs') 89
5.4.4 Outcome variables 91
5.4.5 Additional strengths and limitations of the studies 92
5.5 Ethics 94
5.6 Suggestions for future research 95
6. Conclusions 97
7. References 99
8. Papers 1-3 117
8.1 Errata 117
8.2 Copy right 117
9. Appendices 119

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Trondheim, May 2016,

Kari Schirmer-Mikalsen

List of papers

Paper I: Schirmer-Mikalsen K, Vik A, Gisvold SE, Skandsen T, Hynne H, Klepstad P. Severe head injury: control of physiological variables, organ failure and complications in the intensive care unit. Acta Anaesthesiol Scand 2007 Oct;51(9):1194-201.

Paper II: Schirmer-Mikalsen K, Moen KG, Skandsen T, Vik A, Klepstad P. Intensive care and traumatic brain injury after the introduction of a treatment protocol: a prospective study. Acta Anaesthesiol Scand 2013 Jan;57(1):46-55.

Paper III: Schirmer-Mikalsen K, Vik A, Skogvoll E, Moen KG, Solheim O, Klepstad P. Intracranial pressure during Pressure Control and Pressure-Regulated Volume Control ventilation in patients with traumatic brain injury: a randomized crossover trial. Neurocrit Care 2015. DOI 10.1007/s12028-015-0208-8.

Acronyms

ALI	Acute Lung Injury
ARDS	Acute/Adult Respiratory Distress Syndrome
BTF	Brain Trauma Foundation
CBF	Cerebral Blood Flow
CPP	Cerebral Perfusion Pressure (CPP=MAP-ICP)
CSF	Cerebrospinal Fluid
CT	Computer Tomography
EBIC	European Brain Injury Consortium
$etCO_2$	End tidal Carbon dioxide
FiO_2	Fraction of inspired Oxygen
GCS	Glasgow Coma Scale or Glasgow Coma Score
GOS	Glasgow Outcome Scale
GOSE	Glasgow Outcome Scale Extended
HDU	High-dependency Unit
ICP	Intracranial Pressure
ICU	Intensive Care Unit
ISS	Injury Severity Score
MAAS	Motor Activity Assessment Scale
MAP	Mean Arterial Pressure
MRI	Magnetic Resonance Imaging
PaO_2	Partial pressure of arterial Oxygen
$PaCO_2$	Partial pressure of arterial Carbon dioxide
PC	Pressure Control
PEEP	Positive End Expiratory Pressure
PRVC	Pressure Regulated Volume Control
SAPS 2/3	Simplified Acute Physiology Score 2/3

SOFA	Sequential Organ Failure Assessment
TBI	Traumatic Brain Injury
TV	Tidal Volume
VAP	Ventilator-associated Pneumonia
VC	Volume Control

Sammendrag

Traumatisk hjerneskade: kontroll av fysiologiske variabler, organsvikt og komplikasjoner på intensivavdelingen

Traumatisk hjerneskade eller TBI (traumatic brain injury) er hyppig forekommende over hele verden. Det rammer oftest unge menn i tillegg til at det er en økt forekomst hos den eldre populasjonen. De hyppigste årsakene til traumatisk hjerneskade i Norge er trafikkulykker og fallskader. En betydelig del av pasienter med TBI har behov for behandling på intensivavdelinger hvor primærfokus er å sikre god sirkulasjon og oksygenering til hjernen og derved unngå ytterligere skade. Andre faktorer som blodsukker, elektrolytter, temperatur og ventilasjon kan også påvirke utfallet av hjerneskaden og er derfor viktige å kontrollere i det akutte forløpet etter skaden.

Denne avhandlingen består av 3 studier som alle tar for seg intensivbehandling av hjerneskadepasienter. Studie 1 er en retrospektiv studie som inkluderer 133 pasienter med alvorlig hjerneskade. Vi undersøkte hvorvidt pasientene fikk den intensivbehandling vi ønsket basert på generelle internasjonale retningslinjer for behandling av hjerneskadepasienter. I tillegg observerte vi hvilke komplikasjoner de fikk under intensivoppholdet. Vi fant at avvik fra ønskede respiratoriske og sirkulatoriske variabler var hyppig forekommende og at lavt blodtrykk, forhøyet blodsukker og lavt albumininnhold i blodet var assosiert med et dårligere utfall. I tillegg registrerte vi at lungekomplikasjoner (spesielt pneumoni) var hyppig forekommende hos pasienter med TBI.

Studie 2 er en prospektiv observasjonsstudie som inkluderer 133 pasienter med alvorlig TBI. Vi studerte hvorvidt pasientene fikk den intensivbehandling vi ønsket basert på en nylig innført protokoll for intensivbehandling av pasienter med TBI i tillegg til at vi observerte hvilke komplikasjoner de fikk under intensivoppholdet. Resultatene fra studien viste hyppige avvik fra behandlingsprotokollen vedrørende respiratoriske og sirkulatoriske variabler og at pneumoni var den hyppigst forekommende ekstrakraniale komplikasjonen. Alder, Glasgow Coma Scale (GCS) skår, dilaterte pupiller, Injury Severity Score (ISS), forhøyet intrakranielt trykk (ICP), forhøyet blodsukker og pneumoni var assosiert med et dårligere utfall.

Studie 3 er en randomisert crossover studie som inkluderer 11 pasienter med moderat eller alvorlig TBI med behov for respiratorbehandling. CO_2 i blodet påvirker ICP ved at høy CO_2 gir dilaterte blodkar og økt ICP mens lav CO_2 kan redusere ICP. En stabil ventilasjon med stabil CO_2 kan dermed tenkes å bidra til å stabilisere ICP. Vi undersøkte om en respiratorinnstilling som i teorien gir et mer stabilt minuttvolum (trykkregulert volumkontroll, PRVC) kunne gi en mer stabil ventilasjon av lungene og derved et mer stabilt ICP, enn den respiratorinnstillingen vi hovedsakelig bruker i dag (trykkontroll, PC). Resultatet viste at begge innstillinger var like stabile vedrørende ventilasjon og ICP og vi har som følge av dette valgt å fortsette med PC modus i behandling av denne pasientgruppen.

Samlet bidrar artiklene til å gi oss økt informasjon om hvordan vi behandler pasienter med traumatiske hjerneskader og viktigheten av å gi en mest mulig målrettet behandling slik at utfallet til denne pasientgruppen optimaliseres.

Kandidat: Kari Schirmer-Mikalsen

Institutt for sirkulasjon og bildediagnostikk, DMF, NTNU

Hovedveileder: Pål Klepstad, NTNU

Biveileder: Anne Vik, NTNU

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Summary

Traumatic brain injury: control of physiological variables, organ failure and complications in the intensive care unit

Traumatic brain injuries (TBIs') often involve young people. However, with an increasing age among the population in the western world there is also an increased frequency of the older population suffering from a TBI due to fall injuries. Many of these patients need treatment in intensive care units (ICUs') where the primary focus is to ensure good circulation and oxygenation to the brain thereby avoiding secondary damage. Other factors such as blood sugar, electrolytes, temperature and ventilation can also affect the outcome and are therefore important to control in the acute course after the injury.

This thesis consists of 3 studies concerning ICU treatment of TBI patients. Study 1 is a retrospective study including 133 patients with severe brain injury. We examined deviations from defined treatment goals during the ICU stay based on general international TBI guidelines. We also studied the incidence of extracranial complications during the ICU stay. We observed that deviations from the desired respiratory and circulatory values were frequent and that low blood pressure, elevated blood sugar and a low concentration of serum albumin could be associated with a worse outcome. In addition, lung complications (particularly pneumonia) were frequent in TBI patients.

Study 2 is a prospective observational study including 133 patients with severe TBI. We studied whether the patients receiving ICU treatment fulfilled the target goals defined in a recently introduced TBI treatment protocol at the hospital, and also registered complications during the ICU stay. The results from the study showed that there were frequent deviations

from the treatment protocol regarding respiratory and circulatory variables and that pneumonia was the most frequent extracranial complication. Advanced age, reduced Glasgow Coma Scale (GCS) score, dilated pupils, Injury Severity Score (ISS), raised intracranial pressure (ICP), elevated blood sugar and the presence of pneumonia were all associated with a worse outcome.

Study 3 is a randomized crossover study including 11 patients with moderate or severe TBI treated with mechanical ventilation. It is known that elevated partial pressure of arterial carbon dioxide ($PaCO_2$) dilates blood vessels and increases the ICP while low $PaCO_2$ reduces the ICP. A fixed ventilation with a constant $PaCO_2$ can thus help stabilizing the ICP. In this study we compared pressure regulated volume control (PRVC) ventilation versus pressure control (PC) ventilation. The first strategy would in theory give a more constant ventilation of the lungs and therefore, predictably, a more stable ICP, than PC ventilation. The study showed no significant difference in ventilation with regard to $PaCO_2$ and in ICP. As a result of the study we have chosen to continue with the PC mode in the treatment of this patient group.

Together, these articles contribute to give information concerning the treatment TBI patients receive in the ICU and emphasize the importance of a goal directed treatment to improve and optimize the outcome in these patients.

1. Introduction to study

1.1 Focus / topic

Traumatic brain injury (TBI) is one of the leading causes of death and disability all over the world with an incidence of 235 per 100.000 per year in Europe and a mortality rate of 15 per 100.000 (Tagliaferri et al., 2006). In developed countries, around 12 % of the adult population will suffer from a TBI and the odds of sustaining a TBI is 2.22 higher in men than in women (Frost et al., 2013). The main causes of TBIs' in Europe are motor vehicle accidents and fall injuries. Many of the people suffering from a TBI are young. However, with an increased life expectancy in the western world, there is an increasing trend of older people suffering from a TBI, especially fall injuries (Maas et al., 2008, Andelic et al., 2012, Dams-O`Connor et al., 2013).

The main goal in treating patients with TBI is to secure adequate circulation and oxygenation to the brain to minimize secondary insults and hence improve the long-term outcome. Secondary insults can be divided into early, intermediate and late injuries. Early injury, being the first 24 hrs, with changes due to the energy from the trauma and disturbed cerebral blood flow. Intermediate injury, from one day until several days after the initial trauma and characterized by neuroinflammation. Finally, late injury (days to weeks after the trauma) leading to an increased risk of seizures and epilepsy (Algattas and Huang, 2014, Urbano and Oddo, 2012). The treatment in prevention of these secondary injuries starts at the scene of the accident and continues during the transportation to and management at the hospital, and further during rehabilitation.

This thesis focuses on the Intensive care unit (ICU) management of TBI patients. We wanted to evaluate whether we give the patients the intended treatment and to what extent physiological variables and extracranial complications during the ICU stay have an impact on long-term outcome. Furthermore, we also wanted to optimize and stabilize the respiratory treatment to TBI patients, and evaluate if a stable ventilation can help stabilizing the intracranial conditions and thereby improve the patients' outcome.

In this thesis, since the time frame from the first to the third article is 8 years (from 2007 till 2015) I have chosen to also include studies published during this time period into the "Introduction to study".

1.2 Perspective / Rationale

TBI is often divided into mild, moderate and severe TBI, depending on the patients Glasgow Coma Scale or Glasgow Coma Score, both referred to as the GCS (Teasdale and Jennett, 1974, *Appendix 1*). The GCS is a worldwide used score to grade the motor, verbal and eye response of patients with reduced consciousness, with a scale from 3 to 15 where 3 means no response and 15 means fully awake and cooperative. When the motor, verbal and eye responses are mentioned for each patient the GCS stands for Glasgow Coma Scale (i.e. motor response 1-6, oral response 1-5, eye response 1-4), whereas Glasgow Coma Score refers to the sum of the 3 scores (i.e. score from 3 to 15) (Teasdale et al., 2014). Most of the TBIs' are mild, defined as having a GCS of 13-15 (Teasdale et al., 2014) or 14-15 (Maas et al., 2008), while a moderate TBI defines a GCS of 9-12 (or 9-13) whereas a severe TBI indicates a GCS score of 3-8 (Carney and Ghajar J, 2007, Maas et al., 2008, Teasdale et al., 2014). Patients suffering from a mild TBI are often diagnosed with a concussion either without any

further investigation or after a normal cerebral Computer Tomography (CT) scan (Åstrand et al., 2016). These patients are usually not admitted to the hospital other than if they have additional extracranial injuries that need treatment. However, studies have shown that patients with mild TBI and a normal CT scan can have abnormal findings when examined with Magnetic Resonance Imaging (MRI) that may affect the outcome (Yuh et al., 2013). Patients with mild TBI will not be discussed further in this thesis. Patients with a moderate or severe TBI are usually admitted to the hospital. Depending on the severity of the TBI and whether the patients need treatment for extracranial injuries, patients may get initial surgery followed by treatment in the ICU. The treatment of TBI patients in the ICU is a challenge due to both the severity of the TBI itself, but also due to extracranial injuries and complications occurring during the ICU stay. The effect of extracranial injuries on outcome may be of most importance in patients with a less severe brain injury, since the main cause of death in patients with severe TBI is the brain injury itself (Gennarelli et al., 1989, Leitgeb et al., 2013).

The main focus of TBI treatment in the ICU is goal directed management to prevent secondary injury, often done by controlling the intracranial pressure (ICP) and the cerebral perfusion pressure (CPP). The CPP is the difference between the mean arterial pressure (MAP) and the ICP; CPP= MAP- ICP. According to the Monro-Kellie doctrine, the adult skull is a rigid box and any increase in one of its constituents (the cerebrospinal fluid (CSF), the brain tissue or the blood volume) means a decrease in any of the others (Mokri, 2001). Compensation here is limited and any disruption in one of these compartments such as the occurrence of hematomas, edema or failure to drain CSF can cause a reversible elevation in the ICP, eventually if not compensated for leading to irreversible herniation.

The intensive care treatment of TBI patients usually includes sedation and mechanical ventilation. To secure an adequate CPP, it is important to keep the blood pressure (and hence the MAP) within specific limits, and to avoid elevation of the ICP. However, this is challenging since the TBI may cause development of intracerebral edema and elevation of the ICP while the sedation of the patients may lower the blood pressure and thus reduce the CPP. There are other factors that may influence the course of the TBI such as intracranial events (e.g. continuous intracerebral bleeding with increased hematoma or development of intracerebral edema), changes in physiological parameters (e.g. serum glucose concentration, serum sodium concentration) and extracranial complications. However, it is not well known how much and to what extent each of these factors influences the outcome in TBI patients.

There has been a development from general guidelines how to treat TBI patients in the ICU to more specific, stepwise guidelines, in order to optimize the TBI treatment. However, many guidelines are generally based on expert opinions and Level II and III evidence (Maas et al., 2008, Stocchetti and Maas, 2014). The purpose of this thesis is to study whether we give the TBI patients the preferred treatment, first based on general guidelines available during the first study (Study 1). Then, in the second study (Study 2) we looked at the TBI treatment in the ICU after the introduction of a more specific, stepwise treatment protocol. During both these studies we observed that mechanical ventilation of TBI patients was a challenge due to respiratory complications often occurring in these patients during the ICU stay. Respiratory complications can affect the ventilation and oxygenation which in turn can affect the intracranial conditions. Keeping a constant and stable ventilation is therefore one of the treatment goals in TBI treatment in the ICU. Based on this we decided to do a

randomized clinical study comparing two ventilation modes (Study 3) to investigate if one of these ventilation modes could give a more constant ventilation and thus help to stabilize the intracranial conditions in TBI patients.

1.3 Review of research

Primary and secondary injuries to the Central Nervous System (CNS) are the leading causes of death in people suffering from trauma (Acosta et al., 1998). There has been an increased focus on developing general guidelines concerning treatment of TBI patients in the hospital to improve survival and long-term outcome, in addition to acknowledging individualized management based on patient characteristics and extracranial injuries.

1.3.1 Diagnosing the TBI

If there is a suspicion of a severe TBI, the patient should be transferred to a hospital that has 24 hr. service of CT, ICU and neurosurgical facilities (Maas et al., 1997). In most TBI patients admitted to the hospital, medical imaging with CT and/or MRI is performed to give a more specific diagnosis. The most common CT findings in patients with severe TBI are multiple contusions, traumatic subarachnoid hemorrhage (tSAH), subdural and epidural hematomas (SDH and EDH) and edemas, and the patients often have a combination of two or more of these findings (Leitgeb et al. 2007). CT is a fast and widely available method to diagnose larger injuries such as hematomas and fractures, it is often a part of the acute examination in a multitraumatized patient and helps to decide whether the patients need acute surgery or not. However CT does not diagnose small bleedings and underestimates injuries to the axons, known as traumatic or diffuse axonal injury (TAI/DAI) (Johnson et al., 2013). MRI gives more detailed information about the brain injury, and can expose minor but important

injuries in the brain such as TAI, that occurs frequently after a TBI (Skandsen et al., 2010, Moen et al., 2012). The use of MRI is increasing but it is still usually not used during the acute setting due to several reasons: 1) it is impractical due to the magnetic field and trauma patients often have multiple devices that are not compatible with MRI, 2) it is time-consuming and 3) it does not add more information needed in the acute setting concerning the need of immediate surgery, than what is obtained from a CT examination.

The IMPACT studies consist of a large database of TBI patients from 8 RCT's and 3 observational surveys. They have shown that CT findings (especially the findings of tSAH, SDH and intracerebral hemorrhage (ICH)), as well as Marshall CT classification III and IV to be predictors of poor outcome and mortality in TBI patients. On the other hand, EDHs were associated with a favorable outcome (Murray et al., 2007, Maas et al., 2007). Raj et al. (2014) found similar predictors as the IMPACT studies, except that they could not find tSAH to be a prognostic factor of a poor outcome. Whereas the IMPACT studies used the Marshall CT classification score, Raj et al. introduced a new score, the Helsinki CT score, and found it to be a better prognostic score in TBI patients. There are several CT classification scores but the different scores will not be discussed any further in this thesis.

1.3.2 The TBI guidelines

In this thesis I have focused on TBI guidelines developed in Europe (the European Brain Injury Consortium, EBIC) and the American guidelines (the Brain Trauma Foundation, BTF, and collaborators). In addition, the guidelines developed in Lund, the Lund concept, are discussed. All these guidelines have surgical evacuation of hematomas as first priority after stabilization of ventilation and circulation. There is a general agreement that significant

subdural and epidural hematomas should be evacuated early but there is no consensus on early evacuation of intracerebral hematomas. A recent multicenter study (STITCH Trauma) comparing early evacuation of traumatic intracerebral hematomas with conservative treatment showed a significantly increased 6 months mortality in the initial conservative treatment group (Gregson et al., 2012, Mendelow et al., 2015). However, the study was stopped due to inability to include enough patients (n=170, planned inclusion 840 patients) so no definite conclusions could be made. Even though surgery is prioritized in the EBIC, BTF and the Lund model, further treatment in the ICU differ (*Table 1*).

The European Brain Injury Consortium

The EBIC was founded in 1994. It includes more than 100 European centers focusing on introducing general guidelines for treating and for conducting clinical trials in TBI patients (Maas et al., 1997). The goal is to introduce general TBI guidelines that can function as a "core approach" in addition to more specified patient directed treatment starting at the site of accident and continuing until the rehabilitation phase after the ICU stay. Since the primary injury to the brain is irreversible, the focus is to minimize factors that can worsen the intracranial and extracranial conditions. It includes a rapid diagnose of the injury, intracranial surgery if needed, sedation and mechanical ventilation in the ICU in more severe injuries (to avoid stress and optimize oxygenation, ventilation and cerebral perfusion) and finally control of physiological parameters such as electrolytes, hemoglobin, blood glucose and temperature that may influence the intracranial conditions. Extracranial systemic injuries such as hypoventilation, hypoxia (e.g. due to respiratory depression due to chest injury or reduced consciousness) and hypotension (e.g. due to bleeding) can also affect outcome emphasizing basic ABC approach and are therefore issues involved in the therapy of

neurotrauma patients. The EBIC guidelines were initially based on consensus and expert opinions, but was revised in 1997 in accordance with new research in TBI patients (Maas et al.,1997).

Table 1. Summary of EBIC, BTF and the Lund concepts.

ICU care	**EBIC guidelines 1997**	**BTF 2007 (3rd edition)**	**The Lund concept 2006**
ICP	< 20-25 mmHg Early surgery (evacuate hematomas) Decompressive craniotomy in exceptional cases Mannitol (S-osmol < 315 mmol/l) CSF drainage	< 20-25 mmHg (level II) Early surgery (evacuate hematomas) Mannitol (level II) CSF drainage	< 20 mmHg Early surgery (evacuate hematomas) Decompressive craniotomy if ↑↑ICP despite all other interventions No mannitol and hypertonic saline Avoid CSF drainage (only use if critically ↑ICP)
Sedation and analgesia	Benzodiazepins + opioids Barbiturates if ↑ICP	Benzodiazepins + opioids Barbiturates if ↑ICP (level II)	Benzodiazepins + opioids Low dose barbiturates if ↑ICP
SpO_2	> 95 %	≥ 90 % (level III)	
PaO_2	> 13kPa	≥ 8 kPa (level III)	12-14 kPa
$PaCO_2$	4-4.5 kPa < 4 kPa (if ↑ICP)	Short-term hyperventilation if ↑ICP	4.6-5.2 kPa Short-term moderate hyperventilation if ↑ICP
MAP	> 90 mmHg Inotropes/vasopressor when normovolemic	Systolic BP ≥ 90 mmHg (level II) Vasopressor when normovolemic	Hypotensive therapy (β1-antagonist, α2-agonist) Precapillary vasoconstrictor if ↑ICP Avoid vasopressors
CPP	60-70 mmHg	50-70 mmHg (level II-III)	60-70 mmHg ≥ 50 mmHg accepted when ↑ICP (adults)
Head elevation	No consensus (flat→30°)	Not mentioned	No (max 20° if ICP↑)
Normovolemia	Normovolemia No fluid restriction (except if pulmonary edema)	Normovolemia	Normovolemia Albumin 35-43 g/l Blood transfusions Avoid crystalloids Diuretics
Blood chemistry	Normal	Not mentioned	Hgb 12.5-14 g/dl Avoid hyponatremia
Body temperature	Avoid hyperthermia	Active cooling may have effect if maintained > 48 hrs (level III).	Normothermia Avoid active cooling
Blood glucose	Avoid hyperglycemia	Not mentioned	Normoglycemia (5-8 mmol/l)
Prophylactic antiepileptics	No	No (level II)	Not mentioned
Nutrition	Enteral	Full caloric replacement by day 7 post-injury (II).	Enteral

EBIC, European brain injury consortium; BTF, Brain trauma foundation; ICP, intracranial pressure; CSF, cerebrospinal fluid; SpO_2, pulse oximetry; PaO_2, partial pressure of arterial O_2; $PaCO_2$, partial pressure of arterial CO_2; MAP, mean arterial pressure; CPP, cerebral perfusion pressure; Hgb, hemoglobin.

The Brain Trauma Foundation and collaborators

The Brain Trauma Foundation (BTF), American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS) and other collaborators developed the American TBI guidelines in 1995 with revisions in 2000 and in 2007, the latest including 15 statements concerning TBI treatment (Bratton et al., 2007). These guidelines are evidence based after systematic reviews on the different clinical issues. Class I evidence defines good randomized controlled trials (RCTs), Class II moderate quality RCTs, good quality case-control/cohort studies and Class III defines poor quality RCTs, moderate/poor case-control/cohort or case series/registries and databases (Carney, 2007). However, none of the topics in the BTF 2007 guidelines include level I evidence. The guidelines from the BTF are in general similar to the EBIC guidelines, even though the BTF guidelines are evidence based whereas the original EBIC guidelines have been based on consensus and expert opinions.

The Lund concept

The Lund concept for treating patients with TBI was introduced in 1992-94 (Asgeirsson et al., 1994, Eker et al., 1998). It presumes a disrupted blood brain barrier (BBB) with increased permeability of small solutes due to the injury, leading to increased brain edema. While an intact BBB is semipermeable and controlled by a crystalloid osmotic pressure, a disrupted BBB is depending on a hydrostatic capillary and colloid osmotic pressure. They argue for optimal ICP treatment by keeping the patients normovolemic and moderately hypotensive to reduce the arterial inflow pressure, while keeping the plasma oncotic pressure normal with infusions of albumin and full blood. (Kongstad and Grände, 1999, Grände et al., 2002, Grände, 2006).

1.3.3 ICU treatment of TBI patients

The treatment of patients with traumatic brain injuries includes treatment of both intra-and extracranial conditions that may affect the brain.

The intracranial pressure (ICP) and the cerebral perfusion pressure (CPP)

All guidelines mentioned above are CPP and ICP directed and therefore presumes that the patients are monitored with an ICP transducer. The normal ICP in adults is below 15 mmHg and is regulated by the total volume of cerebrospinal fluid, brain tissue and blood vessels (Stocchetti and Maas, 2014). If the TBI patients are monitored with an ICP transducer, the goal is to keep the ICP < 20 mmHg and to keep an adequate CPP. The exact upper limit for ICP and the exact lower limit for what is an adequate CPP to secure adequate oxygenation and circulation to the brain is not known. The European and American guidelines have recommended a CPP of 60-70 mmHg. However, while the EBIC and BTF tended to initially recommend the upper limit (CPP ≥ 70 mmHg), the Lund concept have accepted a CPP above 50 mmHg. Today, a CPP between 50-70 mmHg in adults represents the most common recommendation. Even though guidelines recommend CPP limits when treating TBI patients, they do not specify what level to use as reference point of the arterial transducer when calculating the CPP (Rao et al., 2013, Bratton et al., 2007). Since many TBI patients are nursed with head elevation to reduce the ICP, measuring the MAP at the heart level gives a higher MAP than the intracranial MAP which in turn affects the calculation of the CPP (Smith, 2015). A recent statement from the councils of the Neuroanaesthesia and Critical Care Society of Great Britain and Ireland (NACCS) and the Society of British Neurological Surgeons (SBNS) now recommends to measure the arterial pressure at the level of the middle cranial fossa, which can be approximated to the tragus of the ear and recommend all

research articles concerning CPP to state the level of the arterial transducer during MAP registrations (Thomas et al., 2015). Since most of the published studies on TBI patients up till now do not mention the level of the MAP transducer when discussing the CPP and the ICP, I have chosen to focus on discussing the ICP and not the CPP throughout this thesis. This has also been done in a review on TBI treatment by Chesnut et al. (2014).

ICP monitoring

In 2013, the Milan consensus conference summarized that ICP monitoring is indicated in unconscious TBI patients with positive CT scan who need sedation, in patients operated with decompressive craniectomy due to elevated ICP and in some patients operated for supratentorial hemorrhages (Stocchetti et al., 2014). According to the American consensus guidelines by the BTF and collaborators, the ICP should be measured in all salvageable patients with a severe TBI (GCS score 3 – 8) and an abnormal CT (level II evidence). ICP monitoring can also be indicated in adult TBI patients with a normal CT scan if they have two or more of the following: age > 40 years, severely affected motor response or systolic blood pressure < 90 mmHg on admission (level III evidence) . This is in accordance with the recommendations from the Participants in the International Multi-disciplinary Consensus Conference on Multimodality Monitoring (Chesnut et al., 2014). Furthermore the BTF points out a transducer connected to the ventricular catheter as the most accurate way to measure the ICP even though parenchymal transducers are also well accepted (Bratton et al., 2007, Vender et al., 2011, Chesnut et al., 2014). Complications from ICP devices (e.g. infection and bleeding) are rare (Bratton et al., 2007).

Head elevation

There is no consensus whether it is best to treat TBI patients in a supine position or if the head should be elevated to reduce the ICP. While a study by Ng et al. (2004) on patients with severe TBI found a decrease in ICP with head elevation up to 30° without any significant decrease in MAP, CPP and cerebral oxygenation compared to no head elevation, a study by Rosner and Coley (1986) showed the most optimal CPP in TBI patients nursed with 0° head elevation. This was due to that the arterial blood pressure at head level was reduced more than the ICP when the head was elevated, thus leading to a lower CPP.

The EBIC 1997 guidelines have no consensus concerning the position of the head but accept head elevation up to 30° to lower the ICP. The BTF 2007 guidelines do not mention head elevation, while the Lund concept recommends 0° i.e. keeping the patients lying flat.

Sedation and analgesia

All guidelines recommend sedation and analgesics to TBI patients who need mechanical ventilation in the ICU. This is done in order to reduce stress and to reduce oxygen demand and hence reduce the ICP. In addition it facilitates a stable mechanical ventilation by making the patients accept the assisted ventilation.

The most common sedatives and analgesics are benzodiazepines and opioids. In addition alfa 2 agonists (clonidine and dexmedetomidin) have recently been introduced as additional sedatives in TBI patients. All these medications, to a more or lesser extent, have a risk of prolonged sedation, hypotension, delirium and constipation (Devabhakthuni et al., 2012). Level of sedation is being assessed by using different evaluation scores. One example is the Motor Activity Assessment Scale (MAAS). This scale goes from 0 to 6 where 0 means that the patient is unresponsive to standardized stimuli (e.g. tracheal suctioning) and 6 means that

the patient is dangerously agitated (Devlin et al., 1999). The goal in the initial treatment of TBI patients needing mechanical ventilation is to keep MAAS 0-1 (from unresponsive to slightly responsive e.g. opening of the eyes).

Oxygen saturation and PaO_2

Low levels of oxygen, hypoxia, causes increased cerebral blood flow due to cerebral vasodilation (Hoiland et al., 2016) and has a negative effect on the outcome in TBI patients (Valadka et al., 1998, Davis et al., 2009, Oddo et al., 2011). However, the exact oxygen limit is not defined. Too high levels of oxygen do not seem to improve brain oxygen metabolism (Magnoni et al., 2003, Diringer et al., 2007) and may also be harmful (Davis et al., 2009). While the BTF and EBIC recommend a pulse oximetry of ≥ 90 and > 95 % respectively, they differ more on the desired level of partial pressure of arterial oxygen (PaO_2) in TBI patients to secure an adequate cerebral oxygenation (BTF ≥ 8 kPa, EBIC > 13 kPa). According to the Lund concept, the optimal PaO_2 level is 12-14 kPa. Measuring the oxygen level in the brain tissue directly ($PbtO_2$) is often used in addition to the pulse oximetry and the PaO_2. Even though the $PbtO_2$ can give good information about the oxygen level in specific brain regions, this measure is dependent on whether the probe is situated in the injured or non-injured part of the brain. Jugular bulb venous oxygenation saturation (SjO_2) is another tool used to indirectly measure oxygenation of the brain (Le Roux et al., 2014).

$PaCO_2$

Elevated partial pressure of arterial CO_2 ($PaCO_2$) causes intracerebral vasodilation which increases the ICP, while too low $PaCO_2$ causes vasoconstriction and decreases blood flow to the brain (Brian, 1998, van Hulst et al., 2002, Mascia et al., 2005, Stocchetti et al., 2005, Asgari et al., 2011). However, it has been shown that some patients with TBI have reduced

CO_2 response and that this can be associated with a worse outcome (Schalen et al., 1991). In order to secure a stable $PaCO_2$, PaO_2 and ICP, most patients with severe TBI and some patients with moderate TBI are initially sedated and mechanically ventilated.

The first randomized study on hyperventilation in TBI patients was done in 1991 by Muizelaar et al. This study showed that prophylactic hyperventilation was not beneficial in TBI patients. In the prehospital setting a study measuring the end tidal carbon dioxide ($etCO_2$) in intubated patients showed a negative effect of hyperventilation on survival in TBI patients (Davis et al., 2004).

The TBI guidelines have shifted from recommending moderate hyperventilation ($PaCO_2$ 4-4.5 kPa) to all patients to recommending normoventilation ($PaCO_2$ 4.5-5.5 kPa) in TBI patients with normal ICP. The reason for this is that even though hypocapnia causes intracerebral vasoconstriction and thereby decreases the ICP, it may cause reduced oxygenation to the already vulnerable brain. It is therefore only recommended to use hypocapnia during a short time period e.g. during transportation to the operation room (*Table 1*).

Control CT during the ICU stay

It can be difficult to evaluate the course of the TBI in sedated patients, especially if they do not have an ICP monitor. It is therefore important to do clinical examinations routinely, including evaluating the pupils. If there is any suspicion of elevated ICP, a new cerebral CT scan should be done immediately. The EBIC 1997 guidelines recommend a follow-up cerebral CT the day after trauma or earlier if indicated since the initial CT often does not give complete information of the intracranial injury (Maas et al, 1997).

Hemoglobin (Hgb)

There is no consensus concerning the optimal hemoglobin level for brain injured patients. Some argue that a lower viscosity (lower Hgb) of the blood improves the microcirculation in parts of the brain at risk (Thomas et al., 1977, Harrison et al., 1981). However, current TBI treatment protocols tend to recommend a higher Hgb level or at least avoiding anemia to secure oxygenation. The Lund therapy (version 2006) argues for keeping the Hgb level at 12.5-14 g/dl in order to improve oxygen transport to the injured brain (Asgeirsson et al., 1994, Grände, 2006). The EBIC guidelines recommend a non-specified "normal" Hgb in the 1997 version (Maas et al., 1997), and the desired Hgb level is not mentioned in the BTF guidelines 2007. In the TBI treatment protocol at St.Olav's University Hospital from 2003 the desired Hgb levels has been 10-12 g/dl, but was changed to > 10 g/dl in the 2016 version (*Table 2*).

Normovolemia and blood pressure (BP)

Trauma patients are at risk of hypotensive episodes due to factors such as blood loss and sedation. Several studies have shown that early (before arriving to the ICU) and late (during the ICU stay) hypotension in TBI patients is associated with an unfavorable outcome (Piek et al., 1992, Chesnut et al., 1993, Manley et al., 2001, Sarrafzadeh et al., 2001, Jeremitsky et al., 2003). In addition, if hypotension is combined with hypoxia the outcome is even worse (Chesnut et al., 1993, McHugh et al., 2007). By keeping the patients normovolemic it is easier to secure an adequate blood pressure and thereby keeping the cerebral perfusion pressure (CPP) within desired limits. The EBIC 1997 prehospital guidelines have been recommending a systolic BP ≥ 120 mmHg in adults and a MAP > 90 mmHg after admission to the ICU (Maas et al., 1997).

Table 2. ICP treatment protocol at St.Olav's University Hospital (February 2016)

Level	Treatment	Definitions	
1	Adequate sedation and analgesia		
	Thiopental/propofol bolus	during procedures	
	15-20º elevation of the head		
	Surgical evacuation of haematoma if indicated		
	Pulse oximetry > 95 %.		
	$PaCO_2$	4.5-5.5 kPa	
	Hemoglobin (Hgb)	> 10 g/dl	
	Normovolemia		
	Normothermia	Temperature ≈ 37ºC	
	Serum Sodium	≈ 140 mmol/l	
	Blood Glucose	5-10 mmol/l	
	Cerebral perfusion pressure (CPP)*	Adult	60-70 mmHg
		Children	40-50 mmHg, depending on age
2	Check level 1!		
	Consider a new CT scan		
	Hypertonic saline 1mmol/ml	Adult	100 ml
	(S-Na < 150 mmol/l)	Children	1-2.5 mmol/kg,
		If infusion	0.05-0.5mmol/kg/hr
	Mannitol 150 mg/ml	Adult	200-300 ml
	(S-Osm ≤ 320 mosm/kg)	Children	0.25-1 g/kg
	CSF drainage if possible		
	Moderate hyperventilation	$PaCO_2$	4.0-4.5 kPa
3	Check level 1 and 2!		
	Consider a new CT scan		
	Decompressive craniectomy (high priority)		
	Increased sedation	Burst suppression	EEG
	Hyperventilation	$PaCO_2$	< 4.0 kPa
	(Hypothermia	Temp 32- 35 ºC)	

ICP, Intracranial pressure; $PaCO_2$, partial pressure of arterial CO_2; S-Na, serum sodium; CSF, cerebrospinal fluid; EEG, electroencephalography. *Zero level of the arterial pressure is by the level of the heart.

Even though all the three guidelines referred to earlier (EBIC, BTF and Lund) recommend keeping the patients normovolemic, the EBIC and BTF guidelines recommend the use of vasopressor for an adequate MAP and CPP. The argument for this is that they believe it is low BP and not high ICP that is the most common cause of reduced CPP. The Lund concept however, recommends hypotensive therapy in normovolemic TBI patients, with additional

precapillary vasoconstrictor treatment to lower the hydrostatic capillary pressure and hence reduce the ICP (Asgeirsson et al., 1994).

Normothermia and hypothermia

Elevated body temperature increases oxygen demand and there is general consensus to avoid hyperthermia in TBI patients. Hypothermia lowers the metabolic rate and hence the oxygen demand and there have been discussions whether TBI patients could benefit from lowering the body temperature in the initial treatment in the ICU. Other possible positive effects of hypothermia may be reduction of the production of free radicals, preventing apoptosis and reduction of edema formation (Polderman, 2008). In children, recent studies have shown no benefit in outcome in TBI patients treated with hypothermia compared to normothermia (Hutchison et al., 2008, Adelson et al., 2013). In adults, some studies have shown better outcome in TBI patients treated with hypothermia (Polderman et al., 2002, Zhao et al., 2011), while others have shown no difference in outcome in patients treated with hypothermia compared to patients with a normal body temperature (Clifton et al. 2011). Clifton et al. discuss whether to cool patients or not may be depending on if the patients have a diffuse brain injury (where cooling may not help) or an intracerebral hematoma (where cooling may help). It may also be that not only hypothermia but also the rewarming procedure may be of importance to avoid rebound elevation of the ICP (Algattas and Huang, 2014). Treating TBI patients with prophylactic hypothermia is however not recommended (Urbano and Oddo, 2012).

The EBIC, BTF and the Lund concepts all agree to avoid hyperthermia, whereas the BTF 2007 guidelines considers hypothermia to be a treatment option with a possible effect. However, this advice was stated before the results from the EUROTHERM3235 Trial were published.

This is a recent multicenter RCT study in Europe, Brazil and India which showed a worse outcome in TBI patients with increased ICP who were treated with hypothermia compared to the normothermia group (Andrews et al., 2013 and 2015). In patients surviving cardiac arrest hypothermia has been recommended as part of the post-resuscitation care. However, a recent multicenter study by Nielsen et al. (2013) on survivors from cardiac arrest showed no benefit when comparing post-resuscitation cooling at a temperature of 33°C with a targeted temperature of 36°C. There is an ongoing study on early cooling of TBI patients (the POLAR-RCT study) in Australia and New Zealand that may give further information on this subject (Nichol et al., 2015).

Serum sodium and hypertonic saline

Many patients suffering from a TBI develop hyponatremia during their ICU stay. This may be due to conditions such as inappropriate secretion of antidiuretic hormone (SIADH), cerebral salt wasting and adrenocorticotropic hormone (ACTH) insufficiency (Kleindienst et al., 2015). A low serum sodium causes an osmotic gradient from the blood over to the brain cells that can lead to the development of cerebral edema. It is therefore of importance to avoid hyponatremia. However, when correcting a low sodium it is important to consider whether the low sodium is acute (which is often the fact in TBI) or chronic, since a rapid correction of chronic hyponatremia may be detrimental due to the risk of developing central pontine myelinolysis (Singh et al., 2014).

None of the guidelines mentioned earlier, have recommendations which serum sodium level to prefer in TBI patients, but agree on avoiding hyponatremia. If the patients develop a critical cerebral edema, one of the treatment options in the acute setting is to infuse hypertonic saline (Kleindienst et al., 2015). Hyperosmolar therapy requires an intact BBB to

have an effect. After a TBI, the BBB may be disrupted in the injured part of the brain. Therefore the osmotic gradient when using hyperosmolar fluids primarily have an effect in the noninjured brain areas (Ropper, 2012). While the BTF 2007 guidelines do not find enough evidence to recommend hypertonic saline in adult TBI patients with elevated ICP (Bratton et al., 2007) it is recommended in the pediatric guidelines as a level III evidence (Adelson et al., 2003). Since the Lund concept is based on a disrupted BBB, they do not recommend the use of hypertonic saline or mannitol.

Mannitol

An alternative to hypertonic saline in treating patients with elevated ICP, is to use mannitol. Like hypertonic saline, mannitol reduces the ICP by increasing plasma osmolarity and then extracts water from the brain. Mannitol also requires a functional BBB (Stocchetti and Maas, 2014). In addition, mannitol works as a dehydrating hyperosmolar fluid by inducing an osmotic diuresis (Ropper, 2012 and 2014). One study of the effect of mannitol on intracranial hypertension found no decrease in cerebral blood volume but a decrease in ICP. They concluded that the effect of mannitol on ICP may be due to reduced intracerebral brain water and not due to reduced cerebral blood volume (Diringer et al., 2012). There is no consensus whether to prefer hypertonic saline or mannitol when treating elevated ICP (Hinson et al., 2013, Todd, 2013). A study by Francony et al. (2008) showed equal effect on reducing the ICP when using hypertonic saline and mannitol. In addition to decreasing the ICP, hypertonic saline increased the serum sodium and the chloride level, while mannitol increased cerebral blood flow and diuresis. Another study showed that hypertonic saline was associated with lower ICP and higher CPP and cardiac output than mannitol in TBI patients with elevated ICP (Oddo et al., 2009). The BTF 2007 guidelines recommend mannitol as a

level II evidence as effective treatment of raised ICP (Bratton et al., 2007). This is in accordance with the EBIC guidelines.

Albumin

There is no consensus on which fluid to prefer in the resuscitation of TBI patients. The Lund concept includes the use of albumin as the colloid of choice (in addition to blood transfusions) (Grände, 2006). Other studies have also found a positive effect of albumin on the brain after focal cerebral ischemia (Belayev et al., 1998). This is in accordance with a systematic review that showed that albumin infusions reduced mortality, disability and neurological deficits in brain injured patients (Haynes et al., 2003). Contrary to this, a post hoc study of TBI patients from the SAFE study (Saline versus Albumin Fluid Evaluation study) showed an increased mortality with fluid resuscitation with albumin compared to resuscitation with saline (Myburgh et al., 2007). One argument against using albumin infusions is that albumin contributes little to the total osmolality compared to serum sodium and therefore the effect of albumin infusions is limited. However, a study by Drummond et al. (1998) showed that even though normal saline increased osmolality, the colloid oncotic pressure decreased and brain water increased. They conclude that a decrease in colloid osmotic pressure without a simultaneous reduction in osmolality may in fact aggravate cerebral edema. The EBIC and BTF guidelines recommend normovolemia with intravenous fluids without specifying this any further.

Serum glucose

In critical ill patients there is an increased sympathetic stress response with increased levels of catecholamine and elevated blood sugar concentrations (Hörtnagl et al., 1980, Collier et al., 2008). One of the changes in the treatment of ICU patients in general during the past few years is the blood sugar regulation. It shifted from avoiding high blood sugar levels to advocating a strict blood sugar regulation after the publication of the Leuven 1 study in 2001 (van den Berghe et al., 2001). This study concluded that keeping the blood glucose at or below 110 mg/dl (6.1 mmol/l) reduces morbidity and mortality in surgical ICU patients.

On the other hand, the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation) study showed that low blood sugar regulations (4.5-6.0 mmol/l) was associated with increased mortality in ICU patients compared to targeting a moderate blood sugar level (≤ 10 mmol/l) (Finfer et al., 2009). There have been several studies on the effect of blood glucose regulation in TBI patients and this will be discussed further in the discussion part of this thesis.

Whereas the BTF 2007 guidelines do not mention the desired blood glucose limits in TBI patients, the EBIC 1997 guidelines recommend avoiding hyperglycaemia and the Lund 2006 model recommends a blood sugar level of 5 - 8 mmol/l.

CSF drainage

One way of controlling and decreasing the ICP is to drain cerebrospinal fluid (CSF). This is an effective method and has been widely used for many years (Srinivasan et al., 2014). The CSF drainage is usually performed via a catheter to the cerebral ventricles. CSF drainage can also be done through lumbal catheters (Tuettenberg et al., 2009), but due to the risk of cerebral

herniation this procedure is now rarely used except in patients with low ICP and chronic CSF leakage. CSF drainage is an option in all guidelines mentioned earlier.

Decompressive craniectomy

In some patients with a severe TBI, the brain injury causes a cerebral edema that is not responsive to any of the treatment options mentioned above. One of the treatment options is then to remove part of the skull to reduce the intracranial pressure, decompressive hemi-/craniectomy (depending on if the operation is uni-or bilateral). The effect of decompressive hemi-/craniectomy is controversial (Kolias et al., 2013). A study by Taylor et al. (2001) on children with critically high ICP showed a better 6 month outcome in children treated with decompressive craniectomy compared to children treated with conventional treatment. On the other hand, even though the Decompressive Craniectomy trial (DECRA study) also showed that ICP was reduced with decompressive craniectomy compared to barbiturates, the mortality was the same and the 6 months neurological outcome was worse in the craniectomy group. However, when adjusting for pupil reactivity, this difference was not significant (Cooper et al., 2011). There is now an ongoing study, The Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) trial, comparing medical treatment to decompressive craniectomy in patients with refractory ICP, but the results have not been published yet (Hutchinson et al., 2006).

The EBIC, BTF and the Lund guidelines recommend decompressive craniectomy in selected cases where the ICP is not controlled with other treatment.

Barbiturate coma

An alternative to decompressive craniectomy in patients with refractory ICP despite other treatment is barbiturate infusion. Barbiturates reduce cerebral metabolism and blood flow and may reduce the ICP. However, it also commonly causes hypotension so the total effect on the cerebral perfusion pressure is probably negligible and there is no evidence that barbiturates affect mortality or long-term outcome (Roberts and Sydenham, 2012, Majdan et al., 2013). Barbiturates also cause an increased infection rate due to reversible leukopenia and granulocytopenia (Stover and Stocker, 1998).

The EBIC, BTF and the Lund model all recommend barbiturates if the ICP does not respond to other treatment (level II evidence). In the TBI treatment protocol in Trondheim, we have gone from using barbiturate infusion in TBI patients with refractory ICP to prioritize decompressive craniectomy as first level 3 treatment (*Table 2*).

1.3.4 Deviations from treatment protocols

There have been several studies comparing the outcomes in TBI patients before and after the introduction of a TBI treatment protocol, showing that the introduction of a detailed treatment protocol improves outcome (Patel et al., 2002, Elf et al., 2002, Clayton et al., 2004, Patel et al., 2005). However, these studies do not give detailed information whether there are any deviations from these treatment goals and if this could influence outcome. Strict compliance to the treatment goals may be difficult to achieve in day-to-day practice in the ICU due to several causes, such as other intercurrent conditions (e.g. respiratory failure, sepsis and heart failure), lack of education of staff, lack of vigilance, insufficient staffing or other organizational issues. Furthermore, although there are studies evaluating the effect of

elevated ICP or reduced CPP on outcome, the consequences of deviations from other physiological variables have not been studied in detail (Robertson et al., 1999, Balestreri et al., 2006, Elf et al., 2005).

1.3.5 Extracranial complications

Extracranial complications in TBI patients are common and the mechanisms causing these complications are complex, involving infections, traumatic injuries to other organs, inflammatory mediators, hormonal changes and disturbed vasomotor control (Acosta et al., 1998, Piek et al., 1992, Dimopoulou et al., 2005). It can be difficult to evaluate whether the extracranial complications are due to the trauma itself or if it is associated with the TBI treatment. Whereas the trauma causes an inflammatory reaction with pro-and anti-inflammatory substances that can lead to systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) (Bone, 1996), the TBI treatment with e.g. barbiturates and vasopressors can cause infections and respiratory complications.

Even though the TBI itself is the most common cause of death in general trauma patients, acute inflammation is the leading cause of death after 72 hrs (Acosta et al., 1998).

The lungs

The most common extracranial complication in TBI-patients during their ICU stay is pulmonary complications, such as pneumonia, Acute Lung injury (ALI) and Acute Respiratory Distress Syndrome (ARDS).

Pneumonia

A prevalence study of infection rate in > 1400 ICUs' (the EPIC study; the European Prevalence of Infection in Intensive Care Study) showed that pneumonia was the most common ICU infection reported and that ICU acquired pneumonia, sepsis and bloodstream infections increased the risk of ICU death (Vincent et al., 1995).

There are many causes of pneumonia in general ICU patients. Acute sick patients may have reduced consciousness due to trauma or disease and are therefore not able to secure their airways, leading to potential risk of aspiration to the lungs. To secure the patients airways, these patients are often intubated and mechanically ventilated and this may also increase the risk of pneumonia (ventilator-associated pneumonia, VAP) (Pelosi et al., 2011). A prospective multicenter cohort study by Cook et al (1998) found that 17.5 % of mechanically ventilated ICU patients (not only neuro-ICU patients) developed VAP. While one study showed that VAP in the neuro-ICU was associated with increased length of stay but not associated with increased mortality (Josephson et al., 2010), data from the Traumatic Coma Data Bank on patients with severe brain injury showed that pulmonary infections was one of the independent predictors of an unfavorable outcome (Piek et al. 1992).

As mentioned earlier, treating TBI patients with barbiturates may also increase the infection rate and risk of pneumonia (Stover and Stocker, 1998). This is found in a study by Bronchard et al. (2004) where barbiturates, aspiration before intubation and nasal carriage of Staphylococcys aureus on admission were independent risk factors of early onset pneumonia in patients with brain injuries.

ALI and ARDS

In 1994, Bernard et al. published the definitions of Acute lung injury (ALI) and Acute respiratory distress syndrome (ARDS) according to the American-European consensus conference on ARDS. Both conditions require an acute onset, bilateral infiltrates on frontal chest radiograph and no signs of heart failure (pulmonary artery wedge pressure ≤ 18 mmHg or no clinical evidence of left atrial hypertension). In addition, in ALI the PaO_2/FiO_2 ratio is ≤ 39.9 kPa (300 mmHg) whereas the more serious condition ARDS have a PaO_2/FiO_2 ratio ≤ 26.6 kPa (200 mmHg). ARDS was earlier called "adult" respiratory distress syndrome, but was changed back to "acute", since the condition also occurred in children. There are different causes of ALI and ARDS (such as pneumonia, sepsis and aspiration) but they all cause an injury to the lung endothelium and epithelium (Bernard et al., 1994).

The mortality rate of patients suffering from ARDS is high. A study by Suchyta et al. (1992) showed a mortality rate of 53 % in 215 patients with ARDS and the most common cause of death was respiratory failure. Another study of 129 ICU patients with ARDS showed a mortality rate of 52 %. However, in this study, the most common cause of death was sepsis and multiple organ failure (Ferring and Vincent, 1997).

Even though the most common cause of death in patients with severe TBI is the brain injury itself, several studies have shown that both ALI and ARDS are associated with increased mortality in these patients (Contant et al., 2001, Holland et al., 2003), while other studies cannot find this association (Treggiari et al., 2004).

In 2012, Ranieri et al. published the Berlin definition of ARDS to replace the ALI/ARDS definitions (the ARDS definition task force), that compared with the old definitions, better

could predict mortality. The condition still needed an acute onset, bilateral infiltrates on chest X-ray (or CT) and edema not fully explained by cardiac failure. The definition ALI was removed and ARDS was divided into three stages based on hypoxia; mild (26.6 kPa < PaO_2/FiO_2 ≤ 39.9 kPa with PEEP or CPAP ≥ 5cmH_2O), moderate (13.3 kPa < PaO_2/FiO_2 ≤ 26.6 kPa with PEEP ≥ 5cmH_2O) and severe (PaO_2/FiO_2 ≤ 13.3 kPa with PEEP ≥ 5cmH_2O) ARDS (Ranieri et al. 2012) (*Table 3*).

Table 3. Definition of ALI and ARDS

		Acute onset	Oxygenation PaO_2/FiO_2 ratio (kPa)	Chest X-ray bilateral infiltrates	Pulmonary artery wedge pressure
AECC (1994)	ALI	+	≤ 39.9	+	≤ 18 mmHg
	ARDS	+	≤ 26.6	+	
Berlin (2012)	Mild ARDS	+	26.6 < PaO_2/FiO_2 ≤ 39.9	+ or + on CT	Check for cardiac failure and fluid overload
	Moderate ARDS	+	13.3 < PaO_2/FiO_2 ≤ 26.6		
	Severe ARDS	+	≤ 13.3		

AECC, American-European consensus conference; ALI, Acute lung injury; ARDS, Acute respiratory distress syndrome; PaO_2, partial pressure of arterial O_2; FiO_2, fraction of inspired O_2.

Other extracranial complications

Even though pulmonary complications are the most common extracranial complications in TBI patients treated in the ICU, there are other complications that may have an impact on outcome. The study by Piek et al. (1992) on TBI patients from the Traumatic Coma Data Bank, showed that in addition to pulmonary infections, sepsis, shock and coagulopathy were significant independent predictors of an unfavorable outcome. Another study by Zygun et al. (2005) showed that extracranial organ dysfunction occurred in 89 % of the TBI patients and that having a non-neurologic organ dysfunction was independently associated with a worse outcome. In both these studies, pulmonary complications were most frequent, followed by

cardiovascular dysfunction and coagulopathy, whereas renal and hepatic failure were rare. Other studies have also found a low frequency of renal complications in TBI patients (Robertson et al., 1999, Polderman et al., 2002), but needs to be taken into consideration since renal failure has been found to be one of the factors that increases mortality in TBI patients (Corrral et al., 2012).

Other factors such as the need of a tracheostomy, epileptic activity, gastric tube feeding and weight loss have also shown to affect long-term outcome in TBI patients (Godbolt et al., 2015).

1.3.6 Mechanical ventilation in patients with TBI

Most of the TBI patients treated in the ICU have reduced consciousness due to the injury and due to sedation and are therefore intubated and mechanically ventilated. Intubation and mechanical ventilation is important to secure the airways, to secure adequate oxygenation to the brain and to eliminate CO_2. As mentioned earlier, as ventilation regulates the $PaCO_2$ and PaO_2 this in turn affects the ICP. The ventilator provides different ventilation modes and the most common are pressure control (PC) and volume control (VC) ventilation. In both these modes it is possible to adjust and to set a desired FiO_2, respiratory rate and positive end expiratory pressure (PEEP).

Volume control (VC) ventilation

In volume control ventilation mode, the flow pattern is constant throughout the inspiration. The doctor in charge can set a desired volume for each breath, the tidal volume (TV), and the ventilator will then adjust the pressure given for each breath to keep a constant TV.

Pressure control (PC) ventilation

In pressure control ventilation, the inspiratory flow pattern is decreasing (decelerating) throughout the inspiration. The pressure given by the ventilator is predetermined by the doctor in charge but the TV may differ (e.g. due to atelectasis, secretions and lung compliance) to keep a constant preset pressure. The decelerating flow pattern is thought to be closer to the normal physiology of the lungs and may give a lower peak inspiratory pressure than VC ventilation (Sjöstrand et al., 1995, Guldager et al., 1997, Alvarez et al., 1998, Burns, 2008), even though some studies did not show any difference (Pierce et al., 1998).

Pressure regulated volume control (PRVC) ventilation

Pressure regulated volume control is a combination of PC and VC in that the inspiratory flow pattern is decelerating as with PC but the ventilator adjusts the pressure during each inspiration based on the pressure/volume relation for the previous breath to secure a preset tidal volume (Sjöstrand et al., 1995). A stable TV given by PRVC ventilation can thus be hypothesized to give a more stable $PaCO_2$ compared to PC, resulting in a more stable ICP, but this has not been studied.

There have been many studies on mechanical ventilation in ICU patients with respiratory failure and there is general agreement that the optimal lung protective mechanical ventilation is to “open the lung and keep the lung open”, by using adequate PEEP, smaller TV and use as low peak inspiratory pressure as possible to avoid barotrauma (Lachmann, 1992). However, this lung protective treatment may come in conflict with the optimal intracranial conditions since using a PEEP that is higher than the ICP and using a low TV may cause an

increased ICP by increasing the intrathoracic pressure or by affecting the $PaCO_2$ (McGuire et al., 1997, Mascia et al., 2005). While the TBI guidelines include desired levels of oxygen saturation and $PaCO_2$ targets, there is no consensus on which ventilation mode to prefer in TBI patients (Maas et al., 1997, Bratton et al., 2007).

1.3.7 St. Olav's University Hospital

After the introduction of the EBIC general guidelines of TBI patients, St.Olav's University Hospital intended to treat the TBI patients in the ICU according to these guidelines. Initially although we had a written protocol, it was not very accurate and did not contain specific information about what treatment should be given highest priority. The treatment was dependent on the decisions made by the neurosurgeon and intensivist treating the patient. Even though the main goal was the same, i.e. good oxygenation, good circulation and avoid elevations in the ICP, there were no specific limits for the different interventions. For instance, one ICU doctor could define a normoventilation in one patient to be $PaCO_2$ 4.5 kPa, whereas another doctor could define a limit of $PaCO_2$ to 4.0 kPa. The limit for giving blood transfusions could for one doctor be a serum hemoglobin of 10 g/dl, whereas another doctor could set the transfusion limit to 8 g/dl. It was during this time period we performed the first retrospective study (Study 1). A few years later (2003) we introduced a written TBI treatment protocol in the ICU, which was placed at each patient's bed, with specific stepwise treatment goals where the level of treatment was depending on the ICP and CPP (*Table 2, latest version 2016*). The treatment protocol was compiled in cooperation between specialists in neurosurgery and specialists in anesthesia and intensive care medicine and consisted of three treatment levels where level 1 was the basic treatment for TBI patients with a stable ICP (ICP < 20 mmHg in adults). This treatment level included sedation,

normoventilation, normooxygenation, normovolemia and normothermia. If the patient's clinical condition got worse, the treatment was increased to level 2 with moderate hyperventilation, drainage of CSF and administration of Mannitol and/or hypertonic saline. The 3rd treatment level was induced if the patients got critically high ICP despite level 2 treatment and included decompressive craniectomy, barbiturate infusion and hypothermia. In the latest version (February 2016) barbiturate infusion was changed to increase in *any* sedation to burst suppression (in EEG) and hypothermia could only be administered in individual cases. With this treatment protocol the neurosurgeon and the ICU doctor in charge of the patient agreed on which treatment level the patient needed. Since the different treatment levels included specific limits for electrolytes, Hgb, oxygen saturation and $PaCO_2$, these limits were not changed according to changes in health personnel. We then did a prospective study (Study 2) under these conditions. The goal was to study if the patients got the desired ICU treatment according to the treatment protocol and whether deviations from desired treatment goals were associated with outcome. We also registered extracranial complications in TBI patients during the ICU stay. During the first two studies we observed that the TBI patients often had pulmonary complications during the ICU stay. The pulmonary conditions can affect the intracranial conditions in that an elevated $PaCO_2$ as well as a low PaO_2 causes cerebral vasodilation and may thus increase the ICP. Hence keeping a stable ventilation and oxygenation with a stable $PaCO_2$ and a stable PaO_2 is desirable. We therefore wanted to compare the mechanical ventilation we normally use in the ICU (PC ventilation) with a ventilation mode that in theory may give a more constant ventilation and thus a more stable ICP (PRVC ventilation). This is the background for Study 3.

2. Aims of study

In patients with traumatic brain injury treated in the intensive care unit, this thesis has the following aims:

2.1 Study 1

To study the frequency of deviations in physiological variables (blood pressure, hemoglobin, blood glucose, body temperature, serum sodium and albumin) in patients with severe TBI using a retrospective study design and to evaluate if these findings are associated with outcome. We also wanted to evaluate the frequency of extracranial complications (pneumonia, acute lung injury, acute respiratory distress syndrome, sepsis, renal failure, bleeding disorder and liver failure) during the ICU/HDU stay.

2.2 Study 2

To study the frequency of deviations in physiological variables and extracranial complications in patients with severe traumatic TBI who were treated according to a stepwise protocol directed at ICP control using a prospective study design and to evaluate if these findings are related to outcome.

2.3 Study 3

To compare pressure control (PC) and pressure regulated volume control (PRVC) ventilation in TBI patients who need mechanical ventilation in order to observe if there is any difference in $PaCO_2$ and ICP between the two ventilation modes.

3. Materials and Methods

3.1 Patients and setting

The three studies were done in the neurosurgical high dependency unit (HDU) and in the neurosurgical and general intensive care units (ICUs') at St.Olav's University Hospital, Trondheim, Norway. This is the only neurosurgical center in a geographical catchment region including 680 000 inhabitants. The studies are an independent work but is part of the interdisciplinary TBI group at St.Olav's University Hospital, where health personnel with different specialties cooperate in the courses of patients with TBI in this health region.

In Study 1 the patients' HDU and ICU charts were retrospectively reviewed during a 5-year period (1998 - 2002) whereas in Study 2 the patients were prospectively screened and included during a 5-year period (Oct 2004 – Oct 2009). In Study 3 the patients were prospectively recruited during a total period of 14 months (Sept 2013 - June 2014 and August 2014 - Jan 2015). The data from the ventilation periods were registered consecutively in a continuous computer documentation system (Picis Critical Care Manager, Wakefield, USA).

Inclusion

In Study 1 and 2, we included all patients with a severe traumatic brain injury, defined as having a Glasgow Coma Scale (GCS) score ≤ 8 before or after hospital admission. Patients with an initial GCS score > 8 before intubation were included if they deteriorated. All included patients with GCS score > 8 had pathological traumatic findings on cerebral CT.

In Study 3 we included patients ≥ 16 years old with a severity of the TBI indicating continuous measurement of ICP, continuous infusions of sedatives and need of mechanical ventilation. This study could therefore also include patients defined as having a moderate TBI.

Exclusion

In Study 1 and 2, patients with a severity of the TBI resulting in that treatment was withheld at the time of admission due to no hope of survival and patients who died due to extracranial injuries within the first 24 h were excluded. Patients who did not consent to follow-up were also excluded.

In addition, in Study 1 patients were excluded if they were not treated in the neurosurgical HDU or general ICU or if there were lack of sufficient medical records. In Study 2, patients were also excluded if they had a low GCS score due to intoxication or if treatment was withheld due to high age and/or other concomitant severe chronic diseases.

In Study 3 patients were excluded if they were pregnant, had an ICP ≥ 25 mmHg > 5 min, an ongoing cerebral antiedema therapy corresponding to level 3 at St.Olav University Hospital TBI therapy guidelines (*Table 2*), an open external drainage of cerebrospinal fluid (CSF), or if they had a clinical pulmonary condition prohibiting changes in respiratory therapy.

3.2 TBI treatment and treatment goals during the study periods

In all 3 studies, mechanically ventilated patients were sedated and given analgesia with a combination of continuously intravenous infusions of midazolam or propofol and morphine, fentanyl or remifentanil. The upper body was elevated 15-20° in Study 2 and 3 but was not specified in the data in Study 1. The desired oxygen saturation according to EBIC was > 95 %

during all the study periods, whereas the $PaCO_2$ limits varied (4-4.5 / 4.5 / 4.5-5.5 kPa in Study 1, 2 and 3 respectively).

Intracranial hematomas were surgically evacuated if indicated. Patients with ICP monitoring had either an intraparenchymal, an intraventricular or a subdural pressure transducer. For hypotension or failure to reach the target CPP, circulatory support was provided with crystalloids (and colloids in study 1) with additional vasoactive agents (dopamine or norepinephrine) as required. For calculating the CPP, the zero level of the arterial blood pressure was at the level of the heart. In Study 1 the target CPP was > 60-70 mmHg (usually > 70 mmHg). The treatment protocol was changed in 2006 where the desired CPP was reduced from 70 to 60 mmHg in adults and age-specific CPP targets were introduced (45-60 mmHg depending on the child's age).

To regulate the blood glucose, continuous infusion of insulin was given if required. The desired blood glucose level during Study 1 was < 8 mmol/l whereas the blood glucose limit was 4.5-6.5 mmol/l and 5-10 mmol/l in Study 2 and 3 respectively.

There was no specific hemoglobin level mentioned in the first study whereas in Study 2 and 3, blood transfusions were given to keep hemoglobin > 10 g/dl. The desired serum sodium level was not mentioned in Study 1 except for avoiding hyponatremia, whereas the desired serum sodium level in Study 2 and 3 was ≥ 140 mmol/l. Avoiding elevated body temperature was a treatment goal during all study periods.

During the first study, the hospital followed the EBIC general guidelines for treatment of severe TBI without a specific step-by-step protocol (*Table 1*). In 2003 we introduced a three-level treatment protocol based on the EBIC and BTF guidelines, where level 1 represented

the basic intensive TBI treatment to control the ICP and CPP and where the treatment level increased to level 2 and 3 if the ICP continued to rise despite level 1 treatment (*Table 2*).

3.2.1 Study 1 and 2

Treatment of elevated ICP

Study 1 (1998 - 2002):

Increased ICP (> 20 mmHg) was treated with increased sedation and analgesia, moderate hyperventilation, osmotic therapy (mannitol and/or hypertonic saline) and CSF drainage. Patients with increased ICP not responsive to this treatment were administered with increased hyperventilation, continuous infusions with thiopental and in some cases hypothermia or steroids. Decompressive craniectomies were not performed during this time period, although the bone flap was not replaced in some patients.

Study 2 (2004 - 2009):

Elevated ICP (> 20 mmHg in adults, > 15 mmHg in children < 1 years old) was treated with increased sedation and analgesia and boluses of thiopental (level 1). Patients with increased ICP not responsive to this treatment were given level 2 treatment, which included osmotic therapy (mannitol and/or hypertonic saline), CSF drainage, moderate hyperventilation ($PaCO_2$ 4 - 4.5 kPa) and moderate hypothermia (35 - 36 °C). If the patients continued to have elevated ICP and low CPP despite level 2 treatment, they were operated with decompressive craniectomy (level 3) or were given continuous infusions with thiopental, extensive hyperventilation ($PaCO_2$ 3.6 - 4.0 kPa), hypothermia (< 35 °C) and lumbal CSF drainage. In a modified version of the treatment protocol in 2006, decompressive craniectomy was set as

first priority in level 3, and from 2008, therapeutic hypothermia was no longer given to children. Steroids were no longer part of the treatment protocol since the results from the large international CRASH trial (corticosteroid randomization after significant head injury) showed no reduction in mortality in TBI patients receiving corticosteroids (Roberts et al., 2004). Patients without ICP monitoring were treated according to level 1.

Deviations from treatment goals: definitions/criteria

The frequencies of physiological observations not within the recommended limits were identified by reviewing all charts during the stay in the ICU/HDU (K. S-M). In Study 2 the data were registered by an intensive care nurse and quality checked by a specialist in anaesthesiology (K. S-M). $PaCO_2$, PaO_2, systolic BP, blood glucose, serum sodium and body temperature were registered as a moderate or severe deviation if deviations were measured ≥ 3 times/day. Hgb was registered as a moderate or severe deviation if the deviation was measured once during the same day, while serum albumin was registered as a deviation if measured low any time during the ICU stay. Simplified acute physiology score 2 (SAPS 2) was calculated for the first 24 h in patients > 18 years (Le Gall et al., 1993, *Appendix 2*).

The definition of moderate and severe deviations from treatment goals are described in *Table 4*. Blood gas analyses, including the measurements of hemoglobin, glucose and electrolytes were initially taken 5-10 times daily, less frequent if/when the patient's clinical condition stabilized. Continuous intra-arterial blood pressure measurements and ICP were documented hourly and at the time of ICP increases. In Study 2, a moderate/severe deviation in ICP and CPP was defined as ICP 21-25 mmHg/ > 25 mmHg and CPP 50-59 mmHg/ < 50 mmHg. For both these variables, a deviation was registered if measured ≥ 3 times a day.

If treatment was terminated due to no hope of survival, vital parameters including ICP after cessation of active treatment were not registered in the database.

Table 4. Study 1 and 2. Definition of deviations from treatment goals

		Moderate	Severe
$PaCO_2$	kPa	5 - 6	> 6
PaO_2	kPa	8 – 11	< 8
Hemoglobin	g/dl	8 - 10	< 8
Blood glucose	mmol/l	8 – 10	> 10
Serum sodium	mmol/l	130 - 135	< 130
Serum albumin	g/l	< 25	
Temperature	°C	38 – 39	> 39

$PaCO_2$, partial pressure of arterial CO_2; PaO_2, partial pressure of arterial O_2.

Organ failure during ICU/HDU stay

The definitions of extracranial complications are given in *Table 5*.

The incidence of organ failure was identified by reviewing the patients' charts and radiologist consultants' evaluation of X-rays, CT and MRI. Complications such as ventilator-associated pneumonia (VAP), pneumonia due to other causes, acute lung injury (ALI), acute respiratory distress syndrome (ARDS) and severe sepsis were noted. A sequential organ failure assessment (SOFA) score of three or four was used to define renal failure, liver failure and a coagulation disorder (Janssens et al., 2000, *Appendix 3*).

Table 5. Study 1 and 2. Definitions of extracerebral organ complications

Complication	Definition
Ventilator-associated pneumonia (VAP)	Artificial ventilation > 48 h, infiltrates on chest X-ray, leucocytes >10 or < 3 x 10^9/l , temperature > 38.5 ºC or < 35 ºC and purulent tracheal secretions
Pneumonia (other than VAP)	As above but start of symptoms before 48 h of respiratory treatment
Acute lung injury (ALI)	Acute respiratory failure, PaO_2/FiO_2 < 39.9 kPa, bilateral infiltrates on chest X-ray and no heart failure
Acute respiratory distress syndrome (ARDS)	Acute respiratory failure, PaO_2/FiO_2 < 26.6 kPa, bilateral infiltrates on chest X-ray and no heart failure
Severe sepsis	Sepsis with organ dysfunction, hypoperfusion or hypotension with adequate fluid therapy.
Renal failure	Serum creatinine > 299 μmol/l or diuresis < 500 ml/ 24 h (adults).
Bleeding disorder	Platelets < 50 x 10^9/l
Liver failure	Serum bilirubin > 101 μmol/l

PaO_2, partial pressure of arterial O_2; FiO_2, fraction of inspired O_2.

3.3 Study 3 (2013-2014)

The 3-level TBI treatment protocol was according to Study 2 except that lumbal catheter for CSF drainage was no longer part of the protocol.

Interventions

The patients entered the study after initial emergency surgery and stabilization in the ICU. All patients were sedated to motor activity assessment scale (MAAS) score 0–1 (Devlin et al., 1999). All patients were ventilated using a Maquet SERVO-i ventilator system V6.0 (Maquet Critical Care AB, Solna, Sweden). After inclusion, the patients were randomized by a web interface to alternating 2-h periods with PC or PRVC ventilation. After each study period, the

patients were crossed-over to the alternative ventilation mode in the next study period after an interval needed for interventions and adjustment of ventilator settings. Each patient was subject to a maximum of six 2-h study periods, i.e., 3 PC and 3 PRVC periods. Before each study period, the ventilator settings were adjusted to achieve $PaCO_2$ within 4.5–5.5 kPa (normocapnia). The relevant adjustments were positive end expiratory pressure (PEEP), respiratory rate (RR), and pressure support above PEEP (in PC) or tidal volume (TV) (in PRVC). The inspiration:expiration (I:E) ratio was set to 1:2 in all patients. The inspired oxygen fraction (FiO_2) was adjusted to achieve oxygen saturation measured by pulse oximetry (SpO_2) above 95 %. Changes in ventilator settings were avoided during each study period, except for the FiO_2 that could be adjusted to maintain $SpO_2 \geq 95$ %. All interventions that could cause changes in ICP such as tracheal suction and change of wound dressings had to be performed before or between the 2-h study periods. Fluid therapy, the use of vasoactive agents, the use of sedatives, and antipyretics were given as required according to the TBI treatment protocol.

A study period was terminated if the ICP was above 20 mmHg for more than 10 min or ICP ≥ 25 mmHg for more than 5 min and rescue therapy (e.g., opening CSF drainage, osmotic therapy, or respiratory intervention) was initiated. The cause of terminating the study period was registered.

Registrations

Patient demographics (age, gender, simplified acute physiology scale 3 (SAPS 3) (Moreno et al., 2005, *Appendix 4*), concomitant diseases, injury history, GCS score before intubation, intracranial CT findings, injury severity score (ISS) (Baker et al., 1974, *Appendix 5*), SOFA

score, surgical interventions, all medications (vasoactive drugs, sedatives, other) and chest X-ray findings within 24 h were registered at inclusion. The following variables were registered at the beginning and during each study period: ICP, CPP, MAAS, ventilator settings, observed TV, RR, peak pressures, SpO_2, PaO_2, $PaCO_2$, end-tidal CO_2 (Capnostat $etCO_2$ sensor, Maquet, Solna, Sweden), intraarterial blood pressure, heart rate, the use of vasoactive drugs (type/dose), serum sodium concentration, blood glucose, and hemoglobin. Observations were registered every 10 min except for blood gases and clinical chemistry, which were obtained every 30 min (Siemens RAPIDLab 1200 Systems or Radiometer ABL 800 Flex).

Pulmonary complications (pneumonia and ARDS according to the Berlin definition) during the ICU stay, ICU length of stay, and in-hospital mortality were also registered.

3.4 Outcome variables

Study 1

The outcome variables in the descriptive part of the study were 1) the frequencies of deviations in blood pressure, hemoglobin, blood sugar, serum sodium, serum albumin, temperature, $PaCO_2$, PaO_2 and 2) the frequency of the following extracranial complications: pneumonia, ALI, ARDS, severe sepsis, renal failure, coagulation disorder and liver failure.

For the prognostic analysis, the primary outcome variable was the 6-month Glasgow Outcome Scale (GOS) (Jennett and Bond, 1975). The GOS score have 5 outcome variables where GOS 5 and 4 represent good recovery and moderate disability, while 3, 2 and 1 represent severe disability, a persistent vegetative state and death (*Appendix* 6). The patients' outcomes were dichotomized into favorable (GOS 5 and 4) and unfavorable (GOS 3, 2 and 1). A second outcome variable was mortality.

Study 2

The outcome variables in the descriptive part of the study were 1) the frequencies of deviations in ICP, blood pressure, hemoglobin, blood sugar, serum sodium, serum albumin, temperature, $PaCO_2$, PaO_2 and 2) the frequency of the following extracranial complications: pneumonia, ALI, ARDS, severe sepsis, renal failure, coagulation disorder and liver failure.

For the prognostic analysis, the primary outcome variable was the 12-month Glasgow Outcome Scale Extended (GOSE) score (Nichol et al., 2011). Whereas the worse outcomes death and persistent vegetative are the same as in GOS, GOSE have 3 additional levels, that divides good, moderate and severe disability in upper and lower subgroups, hence a total of 8 outcome variables (*Appendix 6)*. Of the six patients where 12-month GOSE was not possible to score, three had a valid registered 6-month GOSE score, which was used in the analyses.

Study 3

The primary outcome variable was ICP during the PC and PRVC ventilation periods. The secondary outcome variable was $PaCO_2$. We also analyzed the fluctuations (standard deviations) of ICP and $PaCO_2$ during the study periods with PC and PRVC ventilation.

3.5 Statistics

The statistical analyses have been described in detail in the individual papers. Descriptive statistics were given as mean, median, range, odds ratio, confidence interval and standard deviations or absolute numbers and percentage as appropriate. Multiple logistic regression was used in Study 1 and 2. In the second study, the model was adjusted for the covariates

age, GCS score and pupil dilation. In Study 3 we used a linear mixed effect model with ventilation mode as a fixed effect and study period nested within patient as a random effect (Rabe-Hesketh and Skrondal, 2012). In all three studies a significance level of 5 % was used.

For the analyses, we used the statistical software Statistical Package for the Social Sciences version ver.18 (SPSS Inc., Chicago, IL, USA) and ver.22 (IBM SPSS statistics, Armonk, New York, USA). In addition we used STATA/SE version 11.2 and ver. 13.1 (StataCorp LP, College Station, Texas, USA).

3.6 Ethical considerations

Written informed consent was initially given by the patient's next of kin since the patients were unconscious. For adult patients who regained capacity to give an informed consent, a deferred consent was obtained. The studies were done in accordance with the principles of the Helsinki declaration and were approved by the Regional Committee for Medical Research Ethics, Health region IV, Norway. In Study 3, which was a randomized controlled study, the protocol was registered in clinicaltrials.gov.

4. Results – Summary of papers

4.1 Study 1 – Paper I

Severe head injury: control of physiological variables, organ failure and complications in the intensive care unit.

Aims: to evaluate deviations of physiological variables and see if these deviations could be related to outcome at 6 months. We also studied the incidence of extracranial complications in patients with severe brain injury.

Results: One hundred and thirty-three patients were retrospectively included during a 5-year period (1998–2002) (*Figure 1*). The median age was 32 years (range 1–88 years) and 81 % were men *(Table 6)*. The majority of the TBIs were caused by either traffic (50 %) or fall (35 %) injuries. The Median GCS score before intubation was 6 (range 3–14). The most common cerebral CT findings were contusions (72 %), subdural hematomas (55 %) and subarachnoid hemorrhage (56 %). Most patients had ICP monitoring (84 %) and 48 % had intracranial surgery. About half of the patients (48 %) had other serious injuries, where the most common were trauma to the chest, followed by facial trauma and fractures/lacerations to the extremities. Median Simplified Acute physiology Score 2 in patients > 18 years (n = 112) was 43 (range 14-80). All but 2 of the 133 included patients received ventilator support during the ICU/HDU stay.

The frequencies of severe deviations from the desired values of the physiological variables for at least one treatment day were: $PaCO_2$ > 6 kPa – 25 %, PaO_2 < 8 kPa – 10 %, hypotensive episodes (systolic BP < 90 mmHg) – 20 %, anemia (Hgb < 8 g/dl) – 22 %, blood glucose >10 mmol/l – 26 %, serum sodium concentration < 130 mmol/l – 10%, serum albumin < 25 g/l –

31% and hyperthermia > 39 °C – 24 % (*Figure 2*). Pneumonia was diagnosed in 71 % and ALI/ARDS in 26 % of the patients. Other complications such as severe sepsis (6 %), renal failure (1.5 %), a coagulation disorder (6 %) and liver failure (one patient) were infrequent (*Figure 3)*.

Mortality at 6 months was 25 % (n=33). Nineteen of these patients died of intracranial hypertension. The 6 months GOS showed a favorable outcome (GOS score 4 and 5) in 37 % (n=49) of the patients while 59 % (n=78) had an unfavorable outcome (GOS score 1-3) (missing GOS score n = 6). Age, GCS score, elevated blood glucose and hypotension during the first day were associated with an unfavorable GOS score at 6 months. Age, GCS, hypotension, low albumin and elevated blood glucose during the first day of treatment were associated with mortality at 6 months (GOS score 1).

Conclusions: Deviations of key physiological variables and pulmonary complications were frequent in patients suffering from severe brain injury. In addition to age and GCS score, hypotension, elevated blood sugar and hypoalbuminemia during intensive care treatment may be associated with an unfavorable outcome.

Figure 1. Enrollment study 1

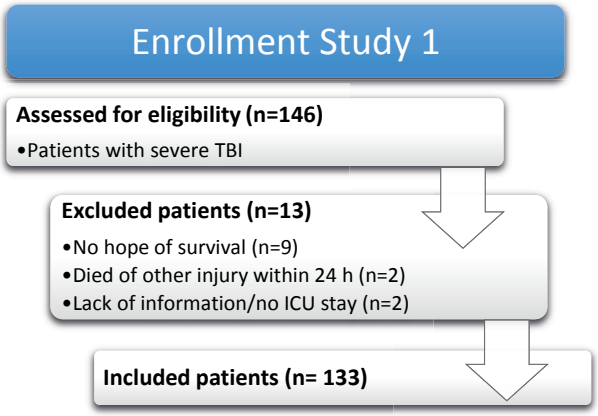
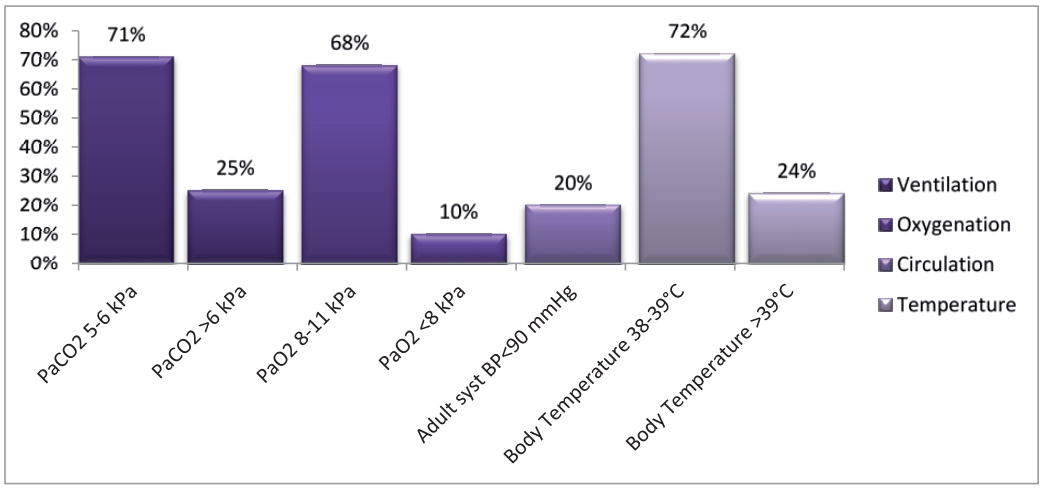


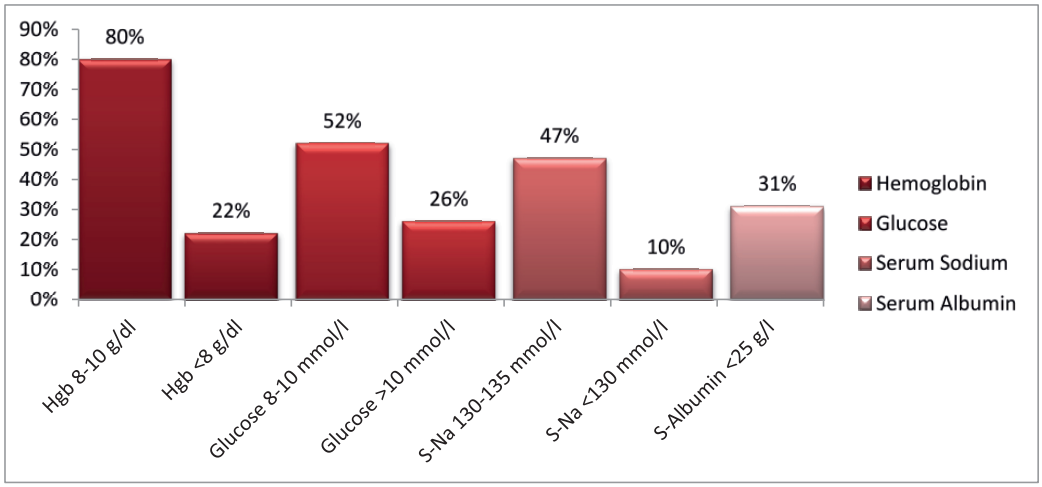
Table 6. Patient demographics Study 1, 2 and 3.

		Paper I (n = 133)		**Paper II** (n = 133)		**Paper III** (n = 11)	
		Number of patients (%)	Median (range)	Number of patients (%)	Median (range)	Number of patients (%)	Median (range)
Sex	Male	108 (81)		106 (80)		9 (82)	
	Female	25 (19)		27 (20)		2 (18)	
Age (years)			32 (1-88)		30 (1-81)		45.5 (16-74)
Cause of accident	Traffic	(50)		70 (53)		7 (64)	
	Fall	(35)		54 (41)		4 (36)	
	Other			7 (5)			
GCS		120	6 (3-14)	131	6 (3-8)	11	5 (3-13)
Pupil dilation on admission		No info		34 (26)		3 (27)	
SAPS 2/3	SAPS 2	112	43 (14-80)	112	43 (21-91)		
	SAPS 3					11	54 (30-75)
ISS		No info		133	26 (5-54)	11	29 (20-45)
Cerebral CT findings	tSAH	(56)		97 (73)		8 (73)	
	SDH	(55)		81 (61)		3 (27)	
	EDH			24 (18)		3 (27)	
	Multiple contusions	(72)		70 (53)		8 (73)	
	Single contusion			7 (5)			
	Normal	0		7 (5)			
Intracranial surgery		(48)		58 (44)		3 (27)	
Extracranial surgery		No info		58 (44)		3 (27)	

GCS, Glasgow coma scale; SAPS 2/3, Simplified acute physiology score 2/3; ISS, Injury severity score; tSAH, traumatic subarachnoid hemorrhage;SDH, subdural hematoma; EDH, epidural hematoma.

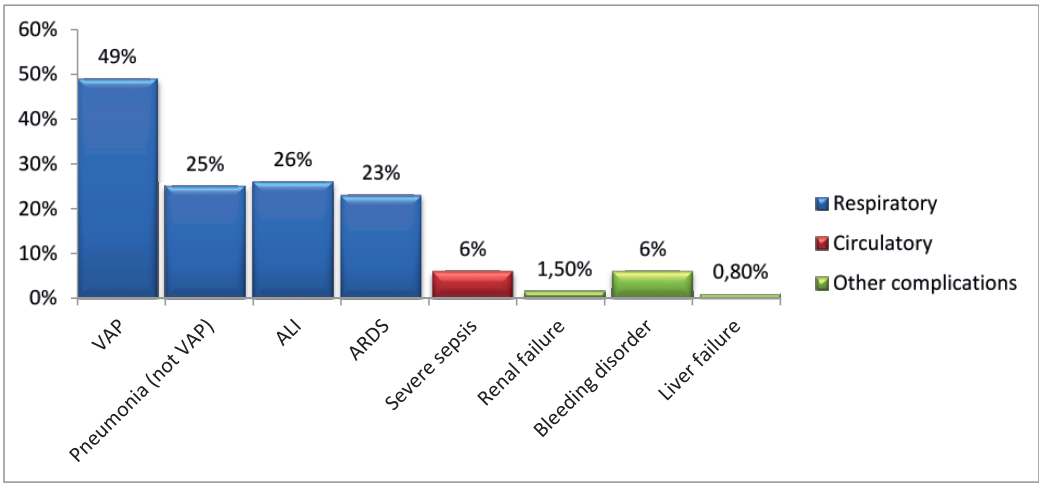
Figure 2. **Study 1**. Deviations from treatment goals*





*Some patients had both severe and moderate deviations in treatment goals and are therefore counted twice.
$PaCO_2$, partial pressure of arterial CO_2; PaO_2, partial pressure of arterial O_2; syst BP, systolic blood pressure.
Total patients with $PaCO_2 \geq 5$ kPa ($PaCO_2$ "5-6 kPa" + ">6 kPa"): 74.4 %, $PaO_2 \leq 11$ kPa (PaO_2 "8-11 kPa" + "< 8 kPa"): 69.2 %, Temperature ≥ 38°C ("38-39°C"+">39°C"): 73 %.
Hgb, hemoglobin; S-Na, serum sodium; S-Albumin, serum albumin.
Total patients with Hgb ≤ 10 g/dl (Hgb" 8-10"+ "<8"): 81 %, Glucose ≥ 8 mmol/l (Glucose "8-10"+ ">10"): 57 %, S-Na ≤ 135 mmol/l (S-Na "130-135"+ "<130"): 48 %.

Figure 3. **Study 1**. Extracranial complications*



*Some patients had both VAP and Pneumonia (not VAP) and some patients had both ALI and ARDS and are therefore counted twice.
Total patients with Pneumonia (VAP+ no VAP): 71 %, ALI+ARDS: 26 %.
VAP, Ventilator- associated pneumonia; ALI, Acute Lung Injury; ARDS Acute respiratory distress syndrome

4.2 Study 2 – Paper II

Intensive care and traumatic brain injury after the introduction of a treatment protocol: a prospective study.

Aims: to evaluate the deviations from a TBI treatment protocol in the ICU and to evaluate the frequency of extracranial complications, and relate these findings to outcome at 12 months.

Results: During a 5-year period (2004 – 2009), 133 patients with severe TBI (GCS score ≤ 8) were prospectively included (*Figure 4*). The median age was 30 years (range 1-81 years) and 80 % were male *(Table 6)*. The majority of the TBIs were caused by either traffic (53 %) or fall (41 %) injuries. The Median GCS score before intubation was 6 (range 3–8). One fourth of the patients (26 %) had uni-or bilateral pupil dilation on admission. The most common cerebral

CT findings were subarachnoid hemorrhage (73 %), subdural hematomas (61 %) and multiple contusions (53 %). In the 7 patients with a normal cerebral CT scan, MRI showed diffuse axonal injury or cerebral contusions. Most patients had ICP monitoring (80 %) and 44 % had intracranial surgery whereas 44 % were operated due to extracranial injuries. Median Injury Severity Score (ISS) was 26 (range 5-54) and median Simplified Acute physiology Score 2 in patients > 18 years (n = 112) was 43 (range 21-91). All but 3 of the 133 included patients received mechanical ventilation during the ICU/HDU stay.

The frequencies of deviations from the treatment goals were: episodes of intracranial hypertension (ICP > 20 mmHg)- 69.5 % (of monitored patients), $PaCO_2 \geq 5$ kPa – 75.9 %, $PaO_2 \leq 11$ kPa – 65.4 %, systolic BP < 90 mmHg - 20.3 %, hemoglobin ≤ 10 g/dl - 77.4 %, serum glucose ≥ 8 mmol/l - 42.9 %, serum sodium ≤ 135 mmol/l - 34.6 %, serum albumin < 25 g/l - 30.8 % and temperature ≥ 38°C – 55 % (*Figure 5*). Pulmonary complications were common (pneumonia 72.2 %, ALI/ARDS 31.6 %). Thrombocytopenia (4.5 %), severe sepsis (3.0 %), renal failure (0.8 %) and liver failure (0.8 %) were infrequent (*Figure 6)*.

Twenty-six (19.5 %) patients died within the first 12 months due to the brain injury, whereas one patient died due to other causes 3 weeks after the TBI. A good recovery (GOSE score 7-8) was seen in 32.3 % (n = 43), a moderate disability (GOSE score 5-6) was seen in 25.6 % (n = 34) whereas 39.8 % (n = 53) had a poor outcome (GOSE score 1-4) (missing GOSE score n = 3). In the multiple logistic regression with age, GCS score and pupil dilation as covariates, ISS, ICP > 25 mmHg, serum glucose ≥ 8 mmol/l and pneumonia were significantly associated with a poor outcome at 12 months (GOSE score 1-4).

Conclusions: Deviations from the TBI treatment protocol were frequent. Pneumonia was the most frequent extracranial complication. Age, GCS score, pupil dilation, ISS, high ICP, hyperglycemia and pneumonia were associated with a poor outcome.

Figure 4. Enrollment Study 2

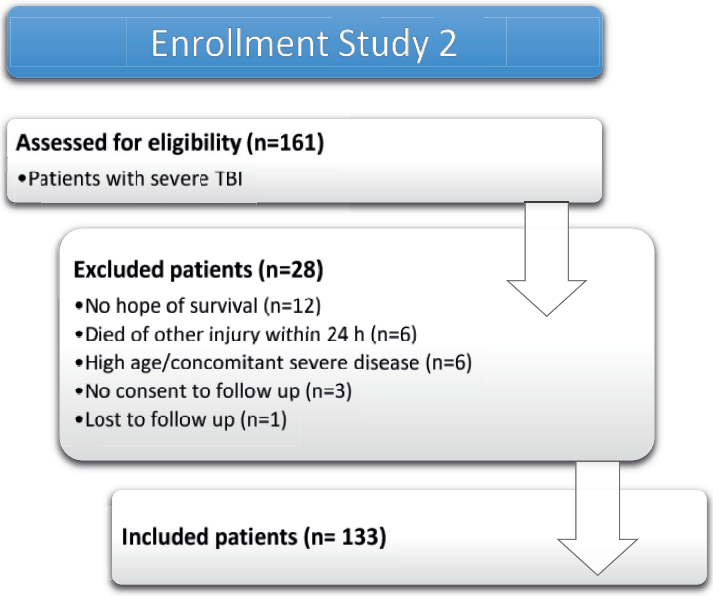
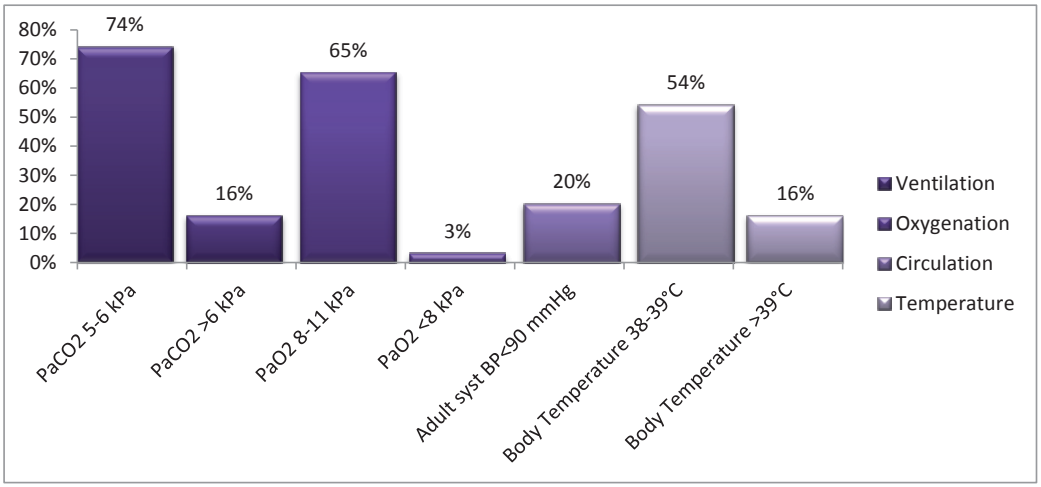
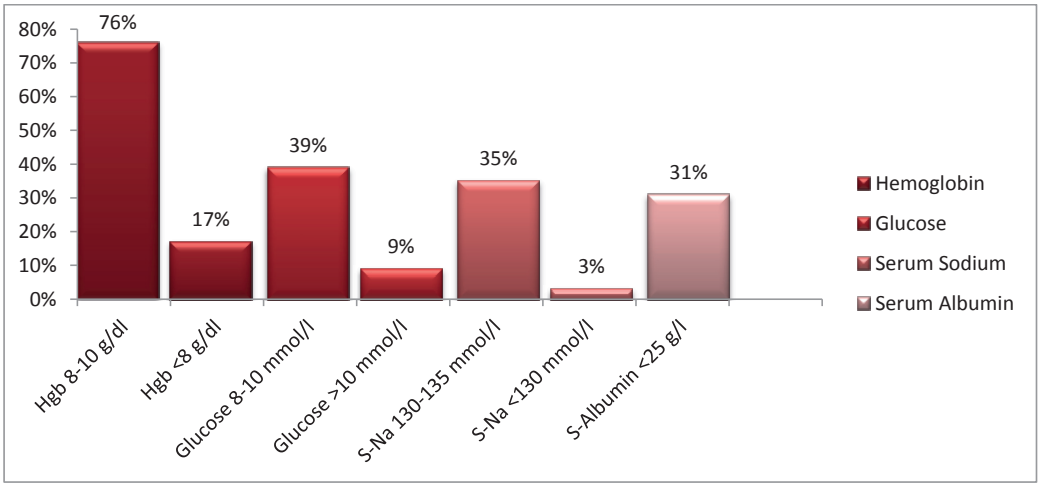


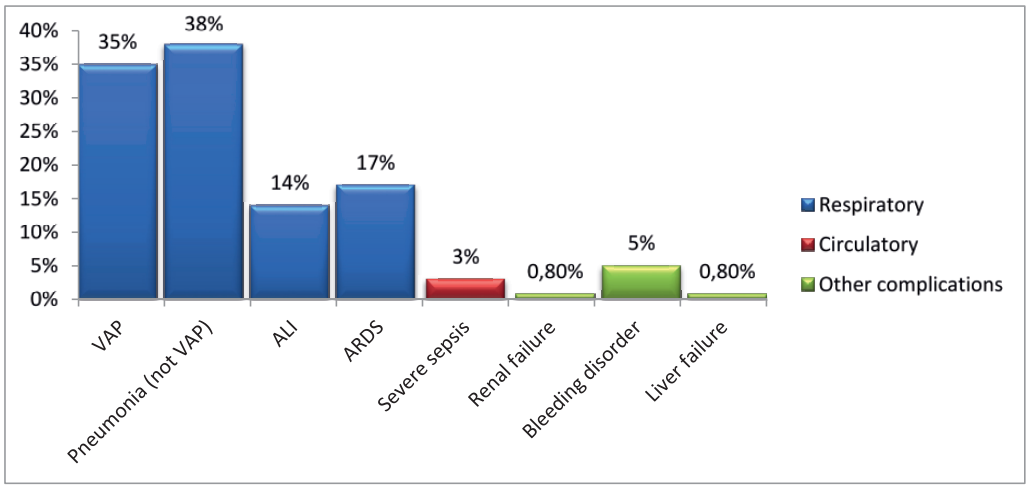
Figure 5. **Study 2**. Deviations from treatment goals*





*Some patients had both severe and moderate deviations in treatment goals and are therefore counted twice.
$PaCO_2$, partial pressure of arterial CO_2; PaO_2, partial pressure of arterial O_2; syst BP, systolic blood pressure.
Total patients with $PaCO_2 \geq 5$ kPa ($PaCO_2$ "5-6 kPa" + ">6 kPa"): 75.9 %, $PaO_2 \leq 11$ kPa (PaO_2 "8-11 kPa" + "< 8 kPa"):65.4 %, Temperature ≥ 38°C ("38-39°C"+">39°C"): 55 %.
Hgb, hemoglobin; S-Na, serum sodium; S-Albumin, serum albumin.
Total patients with Hgb ≤ 10 g/dl (Hgb" 8-10"+ "<8"): 77.4 %, Glucose ≥ 8 mmol/l (Glucose "8-10"+ ">10"): 42.9 %, S-Na ≤ 135 mmol/l (S-Na "130-135"+ "130"): 34.6 %.

Figure 6. **Study 2**. Extracranial complications*



*Some patients had both VAP and Pneumonia (not VAP) and are therefore counted twice.
Total patients with Pneumonia (VAP+ no VAP): 72.2 %, ALI+ARDS: 31.6%.
VAP, Ventilator- associated pneumonia; ALI, Acute Lung Injury; ARDS Acute respiratory distress syndrome

4.3 Study 3 - Paper III

Intracranial pressure during Pressure Control (PC) and Pressure-Regulated Volume Control (PRVC) ventilation in patients with traumatic brain injury: a randomized crossover trial

Aims: to compare two different ventilation modes, pressure control (PC) and pressure regulated volume control (PRVC) ventilation in TBI patients and evaluate if there were any differences in the intracranial pressure (ICP) and partial pressure of arterial CO_2 ($PaCO_2$).

Results: This randomized crossover trial included eleven patients with a moderate or severe TBI who were mechanically ventilated and had ICP monitoring (*Figure 7*). The median age was 45.5 years (range 16-74) and 9 of the 11 patients were men (*Table 6)*. The cause of the accident was either traffic (n = 7) or fall injuries (n = 4). The median GCS before intubation

was 5 (range 3-13). Three of the patients had unilateral pupil dilation on arrival at the hospital. The most common cerebral CT findings were subarachnoid hemorrhage (n = 8), multiple contusions (n = 8), subdural hematoma (n = 3) and epidural hematoma (n = 3). Three patients needed intracranial surgery whereas 3 patients had extracranial surgery. Median Injury Severity Score was 29 (range 20-45) and median Simplified Acute physiology Score 3 in patients > 18 years was 54 (range 30-75).

Each patient was administered alternating 2-h periods of PC and PRVC ventilation. Fifty-two (26 PC, 26 PRVC) study periods were included. The median time interval between two study periods was 70 min. and the median time from adjusting the ventilator settings to the beginning of the observation period was 35 min. Mean ICP was 10.8 mmHg with PC and 10.3 mmHg with PRVC ventilation (p = 0.38) (*table 7)*. Mean $PaCO_2$ was 4.87 kPa with PC and 4.81 kPa with PRVC (p = 0.38). There were less fluctuations in ICP within each ventilation period when using PRVC compared to PC ventilation (residual SD 1.47 mmHg and 1.72 mmHg respectively, p = 0.02). The fluctuations in $PaCO_2$ were also slightly less during the PRVC than during the PC ventilation periods (residual SD 0.27 kPa and 0.33 kPa respectively, p = 0.05).

Conclusions: Mean ICP and $PaCO_2$ were similar for PC and PRVC ventilation in TBI patients. PRVC ventilation resulted in less fluctuation in both ICP and $PaCO_2$ but these differences were very small and of little clinical importance. We cannot exclude that the two ventilator modes would have impact on ICP in patients with higher ICP values; however, the similar $PaCO_2$ observations argue against this.

Figure 7. Enrollment Study 3

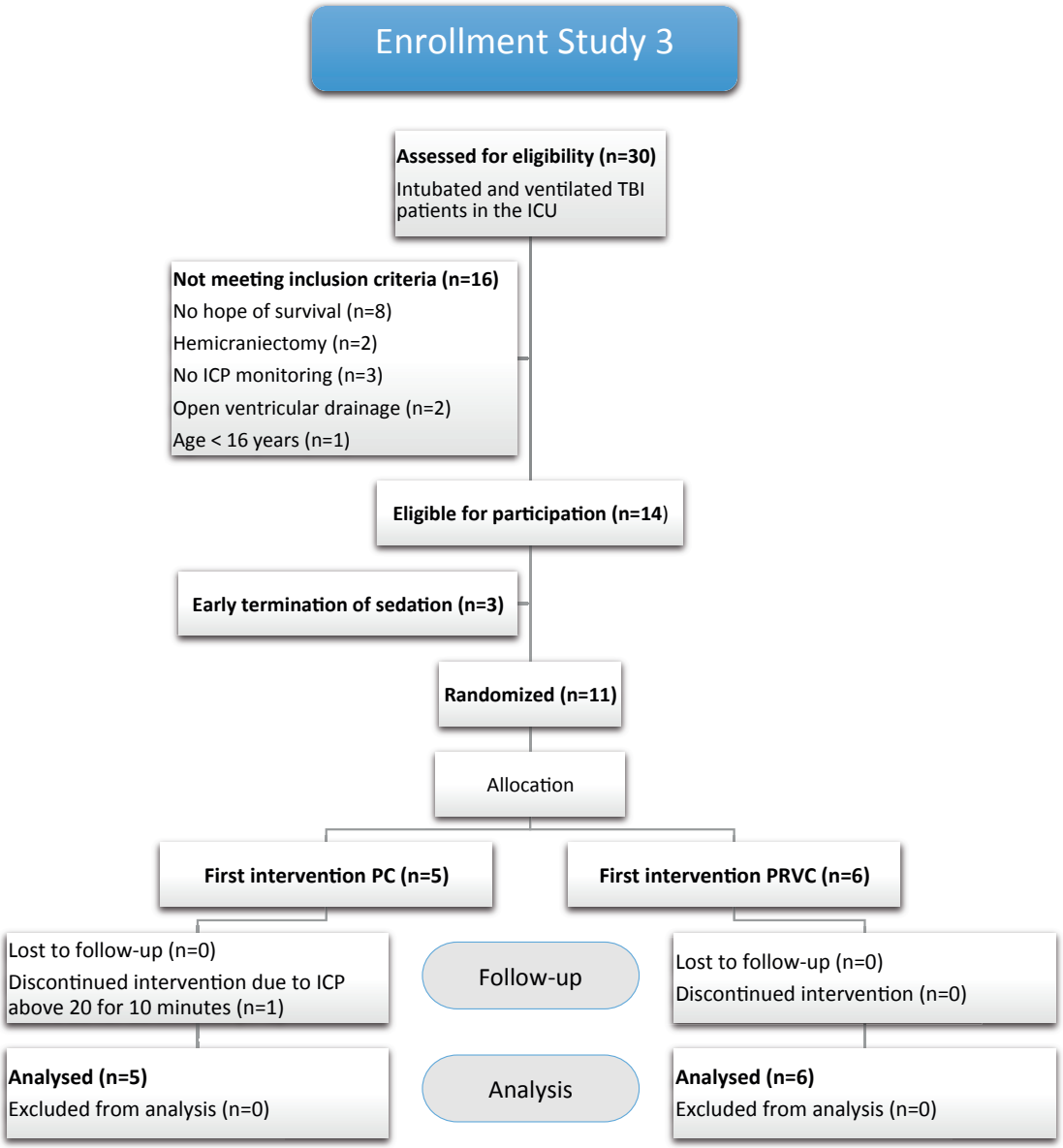


Table 7. Study 3. ICP and $PaCO_2$ from the study periods

Variable	PC	PRVC	p-value[a]	Number of observations. (PC/PRVC)
ICP mmHg				338/336
Mean	10.8	10.3	0.38	
Fluctuations within each study period[b]	1.72	1.47	0.019	
$PaCO_2$ kPa(mmHg)				130/129
Mean	4.87 (36.5)	4.81 (36.1)	0.38	
Fluctuations within each study period	0.33 (2.5)	0.27 (2.0)	0.05	

[a] p-value is derived from a linear mixed effects model with patient as a random effect and ventilation mode as a fixed effect.
[b] Fluctuations are expressed as residual SD within each study period.
PC, pressure control; PRVC, pressure regulated volume control; ICP, intracranial pressure; SD, standard deviation; $PaCO_2$, partial pressure of arterial CO_2

5. Discussion

1) The main finding from the first two studies was that in patients with a severe TBI, there were frequent deviations in physiological values from the treatment goals during the ICU stay. Furthermore, pulmonary complications were common in TBI patients, whereas other extracranial complications were rare.

2) In the first study, age, GCS score, hypotension, elevated blood sugar and low serum albumin were associated with an unfavorable outcome. In the second study, after the introduction of a stepwise TBI treatment protocol, age, GCS score, pupil dilation, ISS, elevated ICP, elevated blood sugar and pneumonia were associated with a poor outcome.

3) The third study compared two ventilation modes (PC and PRVC) in sedated TBI patients and concluded that there was no significant clinical difference in $PaCO_2$ and in ICP levels between each ventilation mode.

5.1 The importance of a TBI treatment protocol

It is recommended that patients with a severe TBI should be treated according to a specific treatment protocol, to improve treatment efficiency (Arabi et al., 2010, Chesnut et al., 2014, English et al., 2013). The treatment protocols in Europe and USA are usually based on ICP

and CPP monitoring. However, not all TBI patients treated in an ICU are monitored with an ICP sensor and there is no consensus on the specific ICP and CPP limits (Bratton et al., 2007, Chesnut et al., 2014). Whereas several studies have shown a relationship between elevated ICP and outcome (Vik et al., 2008, Stein et al., 2011, Balestreri et al., 2006, Stocchetti et al., 2008, Badri et al., 2012), a multicenter RCT could not confirm the benefit of ICP and CPP targeted protocols compared to an imaging and clinical examination based protocol (Chesnut et al., 2012). However, this large multicenter RCT has some issues concerning the generalizability due to different conditions concerning out of hospital treatment. An ICP directed therapy in TBI patients is therefore still preferred (Chesnut et al., 2014).

Our findings indicate that after the introduction of a three-level treatment protocol with more specific treatment goals, there were less severe deviations of certain physiological parameters (such as blood glucose and sodium), while other parameters (e.g. hypotension) remained unchanged. This may suggest that the TBI treatment interventions that can be fairly easy regulated (e.g. regulation of the blood glucose with an insulin infusion) are improved, while other factors may be more difficult to control due to the brain injury itself (e.g. brain edema) and are less prone to be improved. As mentioned by Lingsma et al. (2010), it may also be that deviations in physiological variables are related to the severity of the brain injury, and that normalizing the parameters does not necessarily improve the outcome. This opinion is supported by Patel et al. (2005) who showed that patients with TBI observed between 1996 and 2003 showed less improvement in the adjusted odds of death since 1989 compared to other ICU patients without head injury.

The treatment protocols (Lund, EBIC and BTF guidelines)

As mentioned earlier, the two main TBI treatment concepts in Scandinavia are the Lund concept and the EBIC/BTF concepts (Grände et al., 2006, Nordstrom et al., 2013, Maas et al. 1997, Bratton et al., 2007). There has been one randomized study by Dizdarevic et al. (2012) comparing the Lund concept and the BTF concept showing a lower mortality in patients treated with the Lund concept (43.3 % versus 20 %). However, the mortality rate in the BTF group was unusually high compared to the mortality rate of 25 and 19.5 % in our two first studies when using the EBIC guidelines (which are based on the same goals as the BTF). In addition, a Cochrane review of the Lund concept excluded this study since it did not fully use the Lund concept and they also included patients with spontaneous subarachnoid hemorrhage (Muzevic and Splavski, 2013). They concluded that there is no evidence that the Lund treatment is superior to other TBI treatment models.

The importance of following a protocol

Even though we have TBI guidelines, our studies have shown that it may be difficult to adhere to them. In a study by Lee et al. (2015) the aim was to evaluate if following the BTF protocol would reduce mortality in TBI patients. They concluded that it was difficult to reach all the target goals. Still, when a threshold of 75 % compliance of the BTF guidelines was achieved, it had a positive effect on outcome. However, a compliance rate higher than 75 % had no added positive effect on mortality. This may in part be explained by that the most unstable TBI patients are treated more goal directed and hence all treatment goals are followed. It may also be that not all TBI patients benefit from adhering 100 % to the treatment goals and that treatment should also be individualized (Rosenfeld et al., 2012). Another reason for not adhering 100 % to the treatment goals may be that even though

some interventions can be controlled and improved by the personnel, other factors may be more difficult to control due to the brain injury itself and are therefore less prone to be improved.

5.2 Study 1 and Study 2

Prognostic factors in TBI patients

According to the results from the large Medical Research Council (MRC) CRASH (corticosteroid randomization after significant head injury) and the IMPACT (International Mission on Prognosis and Analysis of Clinical Trials in TBI) studies the three most important prognostic factors on GOS 6 months in TBI patients are age, GCS (GCS motor score in the IMPACT study) and pupil reactivity (Murray et al., 2007, Perel et al., 2008). The association of advanced age and of low GCS with a negative GOS score was as expected also found in our two observational studies (Study 1 and 2). Pupil dilation was not evaluated in study 1, but another study of this patient group showed pupil abnormality to be one of the independent predictors of poor outcome (Vik et al., 2008). This was confirmed in Study 2.

5.2.1 ICP and CPP

In our second study we found that ICP measurements above 25 mmHg was significantly associated with a worse outcome, whereas we could not find this association in patients with episodes of slightly elevated ICP levels (ICP 20-25 mmHg). The association between elevated ICP and outcome was not evaluated in Study 1, but this was done by Vik et al. (2008) on 93 of the 133 patients with a severe TBI included in our study. They calculated the area under the curve (AUC) for ICP above 20 mmHg and found a significant relationship

between elevated ICP and patient outcome and mortality rate at 6 months but it was not a predictor of long-term outcome (> 3 years).

Badri et al. (2012) found that average ICP during the first 48 hrs. of monitoring was an independent predictor of 6 months mortality and that survival seemed to be significantly lower when ICP ≥ 25 mmHg. As mentioned by Treggiari et al. (2007) it may not only be the ICP value but also how the patient responds to ICP treatment that may be important to the outcome. In addition, the risk of cerebral herniation is also depending on the location of the injury (Andrews et al., 1988).

In conclusion, it is important to monitor the ICP and have an ICP directed therapy, although the exact desired ICP level is not known. In addition, elevated ICP should always be considered together with other factors when deciding the treatment level for each patient (Chesnut et al., 2014).

It is a challenge to discuss the CPP since many studies do not document the level of the MAP transducer. In all our studies the MAP transducer was by the level of the heart, which gives a higher MAP and therefor a higher calculated CPP in patients treated with head elevation. Whereas we did not investigate whether the CPP level was associated to outcome, a retrospective study on 127 patients showed that a CPP > 70 mmHg was associated with a lower hospital mortality compared to a CPP according to the BTF guidelines (CPP 50-70 mmHg) (Griesdale et al., 2015). However, they did not mention the level of the transducer.

5.2.2 ICU treatment of TBI patients

Oxygen saturation and PaO_2

In Study 1 and 2 we found that 65-70 % of the patients had episodes of PaO_2 < 11 kPa during their ICU stay even though the desired PaO_2 level was ≥ 13 kPa during both these study periods. However it was not found to be an independent predictor of an unfavorable outcome when adjusting for age, GCS score and pupil dilation. Contrary to this, the results from the IMPACT studies found that hypoxia was one of the predictors associated with an unfavorable outcome (Murray et al., 2007). There may be several reasons for the discrepancy between the desired and registered PaO_2 values in our studies. It may be that the high frequency of pulmonary complications made it difficult to achieve a PaO_2 level > 13 kPa. Another reason can be that the lower PaO_2 values could have been registered during a stable intracerebral condition and therefore accepted since a PaO_2 level down to 9-10 kPa in other ICU patients is generally accepted without calling it hypoxia. In the latest version of the TBI treatment protocol at St.Olav, PaO_2 is no longer mentioned, whereas the desired oxygen saturation is > 95 % (*Table 2).*

We did not study whether patients had episodes of hyperoxia and this could be of importance since hyperoxygenation in TBI patients may be detrimental (Rincon et al., 2014). Contrary to this, there have been studies on the use of hyperbaric oxygen therapy (HBOT) in TBI patients (Rockswold et al., 2013, Algattas and Huang, 2014) but this therapy has not been implemented in the general guidelines (Bratton et al., 2007).

$PaCO_2$

The majority of the TBI patients in Study 1 and 2 had episodes of $PaCO_2$ values ≥ 5 kPa but this was not associated with an unfavorable outcome. Defining a level of moderate hypoventilation to a $PaCO_2$ ≥ 5 kPa was initially appropriate since the desired $PaCO_2$ level in TBI patients was 4.0-4.5 kPa. Since we now define normoventilation to 4.5-5.5 kPa as first level treatment in TBI patients, studies performed today would define moderate hypoventilation with a higher $PaCO_2$ value than we did. What we did register was that there were less severe deviations in several physiological parameters, including $PaCO_2$, in the second study compared to the first study. Whereas 25 % of the patients in the first study had episodes of severe hypoventilation with $PaCO_2$ > 6 kPa, this was reduced to 15.8 % during the second study. We have deliberately chosen not to compare these findings directly since there can be many confounding factors due to different time periods (1998 - 2002 in Study 1 vs 2004 - 2009 in Study 2) including changes in general ICU care. However, introducing a TBI treatment protocol that is always available at the patients bed where the treatment is followed in agreement between the ICU personnel and the neurosurgeons can make it easier to adhere to the protocol.

Hemoglobin (Hgb)

We could not find any significant relationship between anemia and a poor outcome in any of the two observational studies. Even though studies have shown a negative effect of anemia on outcome (Salim et al., 2008) a review by Kramer and Zygun (2009) on anemia and red cell transfusion in neurocritical care concluded that there are no RCTs concerning the transfusion threshold in brain injured patients. A recent RCT by Robertson et al. (2014) found no

difference on outcome when comparing TBI patients treated with a high (10 g/dl) and low (7 g/dl) Hgb level, except for an increased complication rate in patients with the highest Hgb threshold. Likewise, reviews by Desjardins et al. (2012) and Gruenbaum and Ruskin (2014) could not conclude on what is the optimal hemoglobin threshold in neurosurgical patients. A study by Oddo et al. (2012) found that anemia was not by itself associated with an unfavorable outcome, unless it was combined with a low brain tissue oxygen tension. Finally, a review by Kramer et al. (2012) recommend an initial Hgb level > 9 g/dl in TBI patients, but increase the level to > 10 g/dl in patients with a low brain tissue oxygen tension or an increased lactate/pyruvate ratio. In conclusion the optimal Hgb level in TBI patients is not known, but based on the studies mentioned above it may be that the high hemoglobin threshold used today should be reconsidered. On the other hand, since hemoglobin is a carrier of oxygen to the tissue and hypoxia is a well-known factor for a negative outcome (Murray et al., 2007) too low hemoglobin should probably still be avoided.

Normovolemia and blood pressure

Our first study showed that episodes of hypotension could be associated with an unfavorable outcome. This is in accordance with other studies, including data from the IMPACT studies (Murray et al., 2007, Corral et al., 2012, Muehlschlegel et al., 2013). However we could not find this association in our second study. In this study, only 15 patients had episodes of hypotension during the first 24 h in the ICU. Few observations make it difficult to draw conclusions about this finding. Another explanation for this discrepancy can be that we addressed hypotension in the ICU/HDU and therefore did not include hypotension and hypoxia before arriving to the ICU/HDU. Also, during established ICU

treatment, some causes of hypotension such as hypovolemia are usually corrected, and therefore, a low arterial blood pressure may not be associated with decreased cardiac output and lower oxygen delivery. Lately, there has also been focus on avoiding not only hypo- but also hypertensive episodes in TBI patients. This is supported by data from the IMPACT studies where there was a U-shape relation between blood pressure and an unfavorable outcome, indicating that both hypo-and hypertension had adverse effect (Maas et al., 2013). By setting a systolic blood pressure limit of 90 mmHg we were unfortunately unable to evaluate the effect of hypertension on outcome in any of our studies.

Body temperature

Even though normothermia is a treatment goal, elevated body temperature was a frequent finding in both studies and this has also been found by others (Muehlschlegel et al., 2013). We could not observe any significant relation between hyperthermia and a worse outcome but data from the Chinese head trauma data bank found that both degree and duration of hyperthermia are correlated with outcome in TBI patients (Li and Jiang, 2012). In addition, a recent large study from Australia/New Zealand/UK found that having a peak temperature below 37°C and above 39°C the first 24 h during ICU management was associated with increased mortality compared to patients with normothermia (Saxena et al., 2015).

Serum sodium (S-Na)

Hyponatremia was a frequent finding in our studies. Whereas a large cohort study on hospitalized patients found an association between hyponatremia and mortality, we could not find it to be associated with a worse outcome (Waikar et al., 2009). Hyponatremia is the

most common electrolyte disturbance in neurointensive units and can be due to several factors such as iatrogenic (e.g. volume overload with hypotonic fluids, the use of diuretics (including mannitol)), reduced water excretion (as in inappropriate secretion of antidiuretic hormone, SIADH) or increased excretion of sodium (as in cerebral salt wasting, CSW) (Rabinstein and Wijdicks 2003, Haddad and Arabi, 2012). Hyperglycemia may also reduce the sodium concentration due to an osmotic effect. We did not investigate the causes of hyponatremia but one of the causes of low sodium in our patients may be hyperglycemia, since this was frequently occurring in both Study 1 and 2.

Albumin

Hypoalbuminemia in TBI patients is common and was found in almost one third of the patients in our studies. One study suggests that the cause of hypoalbuminemia may in part be due to interleukin-1-induced endothelial cell injury with enhanced endothelial permeability of albumin (McClain et al., 1988). In contrast to the first study, the second study could not find that hypoalbuminemia was associated with a worse outcome. Most studies done on albumin in TBI patients argues pro et con the effect of albumin infusions and do not discuss the desired albumin concentration in the blood. A meta-analysis by Vincent et al. (2003) concluded that hypoalbuminemia in critically ill patients was associated with an unfavorable outcome and that correcting the serum albumin to > 30 g/l was associated with reduced complications. On the other hand a post hoc study from the SAFE study found that the use of albumin infusions in TBI was associated with elevated ICP and increased mortality during the first week after trauma (Cooper et al., 2013). Based on the results from the SAFE study, Vincent et al. (2014) now advice against using albumin in TBI patients.

Serum glucose

Hyperglycemia was found to be one of the factors associated with an unfavorable outcome in both Study 1 and 2. In TBI patients there have been several studies showing a negative effect of elevated blood sugar on outcome (Rovlias and Kotsou, 2000, Salim et al., 2009) although this association could not be confirmed by others (Muehlschlegel et al., 2013). It is uncertain whether it is the blood glucose itself that is harmful to the brain or if the blood glucose level reflects the severity of the TBI (Lingsma et al., 2010). Even though there is no conclusion about the optimal blood glucose level for TBI patients (Oddo et al., 2008, Meier et al., 2008, Bilotta et al., 2009, Green et al., 2010), two recent reviews conclude that a tight glucose control should be avoided to minimize the frequency of hypoglycaemia (Marion, 2009, Bilotta and Rosa, 2010). This is supported by Vespa et al. (2012) who advise against too strict glycemic control, since their study found an increased glucose metabolism in TBI patients with strict glucose control compared to patients with loose glucose control. They conclude that an increase in glucose metabolism when there is limited supply of glucose can be harmful and should be avoided.

5.2.3 Extracranial complications

The lungs

Pneumonia

We found that an overwhelming part of the patients included in our studies acquired pneumonia during their ICU stay and in the second study we found that pneumonia was one of the factors that was associated with a worse 12-month outcome. This is in accordance with a study by Kesinger et al. (2015) who found that pneumonia was an independent factor

of an unfavorable 5-year outcome in TBI-patients. In addition, the large Extended Prevalence of Infection in Intensive Care (EPIC II) study showed that ICU patients with infections had a higher mortality than non-infected patients and that respiratory infections were the most common infections in this study (Vincent et al., 2009). Contrary to this, other studies found that respiratory complications were associated with an increased length of stay but were not associated with an unfavorable outcome in TBI patients (Zygun et al., 2006, Corral et al., 2012).

As mentioned earlier, an increased infection rate in TBI patients may be due to the use of barbiturates (Stover and Stocker, 1998). However, we did not find any significant difference in the incidence of pneumonia in patients treated with and without barbiturate infusion (Study 1).

Pelosi et al. (2011) found an increased rate of VAP in TBI patients compared to other mechanically ventilated ICU patients. It has been speculated that one of the reasons for this may be that the trauma may cause an increased sympathetic response with an associated inflammatory response that can affect both the lungs and the brain (Pelosi and Rocco, 2011). There are different definitions of pneumonia mainly depending on the cause of pneumonia. In our studies we defined ventilator associated pneumonia (VAP) and pneumonia due to other causes. However, when analyzing the associations between pneumonia and outcome in Study 2 we chose to evaluate the two causes of pneumonia as one entity. One of the reasons for this approach is that it is difficult to separate these two conditions. To make it easier to better define VAP, a recent article by the Ventilator-Associated Pneumonia Surveillance Definition Working Group (from The Centers for Disease Control and Prevention) (Magill et al., 2013) suggest new definitions of VAP and stages before the

development of VAP (VAC: Ventilator associated condition, IVAC: Infection-related ventilator-associated complication and finally possible and probable VAP). The reason for this is that by making strict definitions it can be easier to compare VAP between hospitals and it would be easier to follow up and report VAP as a hospital acquired complication.

Acute lung injury and acute respiratory distress syndrome (ALI and ARDS)

The second most prevalent complications in our studies were ALI and/or ARDS. Despite a high frequency of ARDS in Study 2 there were few patients with episodes of severe deviations in PaO_2 during their ICU/HDU stay. This may suggest that the respiratory complications are usually possible to compensate for with ICU respiratory interventions. It is well known that there is a correlation between respiratory complications and mortality (Acosta et al., 1998, Vincent et al., 2009). Whereas we could not find an association between ALI and ARDS on outcome in TBI patients, other studies have shown an increased mortality rate in these patients (Mascia et al., 2008, Rincon et al., 2012). The conventional TBI treatment includes the use of vasoconstrictors to keep an optimal cerebral perfusion pressure and this induced hypertension may be associated with an increased rate of ARDS (Robertson et al., 1999, Contant et al., 2001). Even though all patients with ARDS in our (second) study were given vasoconstrictors we cannot conclude that vasoconstrictor therapy was associated with increased risk of ARDS since most of the patients in this study received vasoactive medications. We did not assess if the use of vasoconstrictor was given to increase the CPP or due to circulatory instability or to counteract hypotension caused by sedation.

Other extracranial complications

Even though the patients in our studies had a high frequency of pulmonary complications, we registered few other extracranial complications, including severe sepsis, renal failure, coagulation disorder and liver failure. Contrary to our findings, a retrospective study by Corral et al. (2012) found that as many as 75 % of TBI patients developed sepsis during the ICU stay whereas 68 % had respiratory infections and 8 % had acute renal failure. According to their study extracranial complications increases the length of stay and morbidity in the ICU but do not increase mortality, with the exception of acute renal failure and hypotension in patients with a low GCS. The discrepancy in the frequency of sepsis between their and our studies cannot be fully explained by different definitions of severe sepsis, since we both use definitions based on the American college of chest physicians/Society of critical care medicine consensus conference (Bone et al., 1992). There is now an ongoing systematic review by Scott et al. (2013) to evaluate the occurrence of infections in TBI patients that may give more information about the epidemiology of infections and help us to improve patient management.

Additional injury and the Injury severity score (ISS)

Many of the included patients in our studies had extracranial injuries and in the second study we found that elevated injury severity score (ISS) was associated with a worse outcome. According to Baker et al. (1974) the ISS is a ".. numerical description of the overall severity of injury in persons who have sustained injury to more than one area of the body.", and also includes the severity of the brain injury. Using a well-established score is important since it makes it easier to compare patient demographics in different studies. Whereas we did not compare outcome in TBI patients with and without extracranial injuries, data on TBI

patients from the Trauma Audit and Research Network (TARN) in the UK found extracranial injuries to be one of the predictors of outcome in addition to age, GCS, pupillary reactivity, hypoxia, and brainstem injury (Lesko et al., 2013). Contrary to this, a study by Sarrafzadeh et al. (2001) showed no difference in outcome between patients with a severe TBI with and without extracranial injuries. A large multicenter study by Gennarelli et al. (1989) concluded that brain injury is the largest contributor to mortality in trauma centers and that the importance of extracranial injuries on outcome is of greatest concern in patients with mild and moderate TBI whereas in patients with severe TBI the complications from the brain injury itself overrules any effect from other injuries.

Finally, the Prospective Observational COhort Neurotrauma (POCON) registry that includes 415 patients with moderate or severe TBI (Lingsma et al., 2013) found that adding extracranial complications to the prognostic IMPACT model could improve the model in patients with a moderate TBI.

5.3 Study 3

5.3.1 Mechanical ventilation in patients with TBI

The importance of positive end expiratory pressure (PEEP) and tidal volume (TV)

There have been several studies on the effect of using PEEP when ventilating TBI patients. PEEP is important in mechanical ventilation since it facilitates in keeping the alveoli open (Vargas et al., 2014). Elevated PEEP may have an adverse effect on the ICP and blood pressure since an elevated PEEP may cause an increase in the intrathoracic pressure which in turn can reduce the cerebral venous return and thereby increase the ICP and lower the blood pressure. Contrary to this a recent study by Nemer et al. (2015) on TBI patients with

ARDS found a better cerebral oxygenation when using a higher PEEP (10-15 cmH_2O) compared to a lower PEEP (5 cmH_2O) without increasing the ICP or decreasing the CPP. According to Mascia et al. (2005) the effect of PEEP in TBI patients is dependent on whether PEEP causes hyperinflation of the alveoli or whether it causes alveolar recruitment. Whereas PEEP in hyperinflated alveoli causes an increased $PaCO_2$ and elevation of ICP, PEEP did not have this effect when it caused recruitment of alveoli. In this study a PEEP level of 10 and 5 cmH_2O were used, whereas we used a PEEP of 5-12 cmH_2O in Study 3.

A less studied issue when ventilating TBI patients is the tidal volume (TV). A study by Mascia et al. (2007) showed that high TV was one of the factors associated with an increased risk of getting ALI/ARDS in TBI patients in the ICU. That high TV should be avoided is strongly recommended after the conclusions from the ARDS network (2000); a multicenter study that showed an increased mortality rate in ALI/ARDS patients treated with high TV (12 ml/kg) compared to a lower TV (6 ml/kg).

In conclusion, since TBI patients are at risk of developing respiratory complications it is important to use a lung protective ventilation with higher PEEP and low TV while trying to keep $PaCO_2$ within normal limits or even accept hypercapnia (given that brain monitoring such as ICP monitoring or brain tissue oxygen tension is used) (Young et al., 2010, Mascia 2009, Lowe and Ferguson, 2006).

5.3.2 PC versus PRVC ventilation

In the third study we compared two different ventilation modes (PC and PRVC), while trying to keep the PEEP and the TV equal in both modes. The main finding was that there was no

difference in ICP and $PaCO_2$ when comparing pressure control (PC) to pressure regulated volume control (PRVC) ventilation in patients with a moderate or severe TBI.

There is no consensus on which ventilation mode to prefer in TBI patients. Even though both PC and PRVC use a decelerating flow and hence are thought to be closer to the normal physiology of the lungs, many still recommend the use of volume control to secure a stable ventilation and hence stable $PaCO_2$. A multicenter study by Pelosi et al. (2011) found that the most common ventilation mode in TBI patients was volume-cycled assist-control ventilation, whereas the use of PC and PRVC were less frequent. While the ICP and $PaCO_2$ were similar when using the two ventilation modes, we observed less fluctuation in ICP and $PaCO_2$ when using the PRVC mode. However, the difference in absolute numbers was small and probably of no clinical importance, demonstrating that both ICP and $PaCO_2$ were relatively stable in both PC and PRVC ventilation. Based on these findings, short-term changes in pulmonary compliance seems to be infrequent in stable sedated TBI patients and hence both ventilation modes give a stable ventilation. However, since this study was done in TBI patients with a relatively low ICP and since the study periods were only 2 h we cannot exclude that there could have been a different finding if the study was done in unstable patients with higher ICP or if the study periods were longer in duration.

There is a large discrepancy between the scientific evidence and regulations needed when introducing new technical devices and settings compared to the introduction of new medicines. The fact that we could not find any previous studies comparing PC, PRVC and VC ventilation modes in respect to their influence on ICP in neurocritical care is one example of this lack of evidence regarding a central component in intensive care.

5.4 Methodological considerations

5.4.1 Single center studies versus multicenter studies

All three studies were done in a single center and the last study included few patients. Performing studies in only one center usually means that fewer patients are included. Due to this and since there may be differences in treatment between different hospitals and patient demographics may differ in different regions, this may reduce the generalizability of the results. On the other hand patients treated in the same center may get more equal treatment, lowering the between patient treatment differences that may influence outcome.

5.4.2 Observational studies

Study 1 and 2 were both observational studies and can therefore only describe associations between different variables and outcome and no causal effect. One of the reasons for this is that there may be other factors that are not investigated that may influence the outcome (confounders) (Sessler and Imrey, 2015). Observational studies can be retrospective or prospective. Retrospective studies have lower reliability since data that are not written down or information that is not remembered are lost and hence give missing data. In addition, it is not possible to check if rare findings are true or just artifacts. Study 1 was a retrospective study and the second study was prospective. However, there was no difference in the number of missing data between these two.

A positive effect of observational studies is that they often use long-term outcome variables (such as GOS and GOSE) compared to randomized control studies.

5.4.3 Randomized controlled studies (RCTs')

Randomized controlled trials are considered the gold standard of clinical trials. By randomizing patients into different treatment groups or by randomizing the order of two different treatments given to the same patient (as in crossover trials), selection bias is avoided. RCTs' are prospective, interventional studies and it is possible to detect a causal relationship between the intervention and the outcome (Sessler and Imrey, 2015). According to the BTF, good RCTs' should include the following: adequate random assignment method, allocation concealment, groups similar at baseline, outcome assessors blinded, adequate sample size, intention-to-treat analysis, follow-up rate 85 %, no differential loss to follow-up and maintenance of comparable groups (Carney, 2007). It is very difficult to adhere to all these criteria when performing clinical studies and therefore most of the guidelines in TBI treatment are based on less evidence. In our third study, the researcher was blinded to the sequence of interventions before the patients were included and received the randomization by a web interface (performed by Unit for Applied Clinical Research, NTNU, Trondheim, Norway) after inclusion. Even though the interventions (PC and PRVC) were not possible to blind to the investigators during the study periods, it was blinded to the statistician assessing the outcome data. In addition, by adjusting the ventilation modes to normoventilation (with a $PaCO_2$ level of 4.5-5.5 kPa) during a baseline period before the beginning of all study periods, and by giving the patients both treatments (the crossover design) we tried to make the conditions between the two interventions as equal as possible. No patients were lost to follow up and the groups were comparable.

Crossover trials

Crossover trials defines a subgroup of RCTs' and was used in Study 3. In these trials each patient gets both interventions that are studied with a time interval between the two interventions. The patients can get each intervention once or several times. By using the patients as his/her own control, the findings in our third study were less influenced by inter-individual variability e.g. due to differences between the patients' pre-injury characteristics or their acute illness. This design requires less patients than RCT's with two different patient groups thereby making it easier to complete the study in the estimated time frame. However, since the patients got both ventilation modes we could not use long-term outcome variables (e.g. mortality or disability) but had to use surrogate endpoints (ICP and $PaCO_2$). There are several important issues to consider when doing crossover trials. Firstly, the length of each treatment period is important. Since we could not find any similar studies we used 2 h intervention periods so that other interventions (such as changes in position or tracheal suction) that would confound the observations could be postponed till after the study period. Also Guldager et al. (1997) who compared VC and PRVC in patients with acute respiratory failure without intracranial pathology used 2 h study periods. Secondly, there is a risk that the effect from the first intervention can affect the second intervention (carry-over effect) (Peacock and Peacock, 2011). It is difficult to decide how long the time interval between two interventions should be. Whereas the effect from different medications can have effect for days, adjustments in mechanical ventilation usually give a much quicker response in the lungs. The median time interval between two study periods was 70 minutes and the median time from adjusting the ventilator settings to the beginning of the intervention period was 35 minutes and was considered to be adequate. Finally, in order to

perform crossover trials the patients' clinical condition needs to be stable. Getting a potential effect on ICP by a given treatment in patients with a relatively normal ICP is difficult due to the pressure-volume relationship in the brain (the Monro-Kellie hypothesis (Mokri, 2001)). However, it is of importance to perform studies in less vulnerable patients before introducing a new treatment to unstable and critically injured TBI patients. Our study thus works as phase 2 trial which is a small RCT to test the effect of an intervention in a few patients.

5.4.4 Outcome variables

GOS and GOSE

Glasgow outcome scale (GOS) and Glasgow outcome scale extended (GOSE) scores are both widely used long-term outcome variables in clinical research and were used in our observational studies. Using well-known outcome scales improves the generalizability of the studies. In addition, using long-term outcomes is more valuable than short-term outcomes since many TBI patients may improve their clinical condition markedly from early to late rehabilitation phase. In Study 1 we used GOS score at 6 months while we in the second study used GOSE score at 12 months. Whereas we dichotomized the outcome variables into favorable and unfavorable in Study 1, this was improved in Study 2 by reclassifying GOSE into three groups (worse outcome, moderate disability and good recovery). This gives increased power, compared to a dichotomized outcome (Hall et al., 2012).

Surrogate endpoints

A surrogate endpoint is a substitute for a clinical endpoint (e.g. mortality and GOS) when this cannot be used (Hall et al., 2012). The surrogate endpoint should however be associated

with a meaningful clinical outcome measure (Hulley et al., 2013). In the 3rd study we used ICP and $PaCO_2$ as surrogate endpoints. Since this was a crossover study where the patients got both treatments (PC and PRVC) it was not possible to have a clinical endpoint such as mortality or GOS. However, since several studies have shown a negative effect of elevated ICP on outcome, we found it reasonable to use ICP as our primary outcome variable.

5.4.5 Additional strengths and limitations of the studies

Limitations

1) We did only register deviations during the ICU stay. It is also of major importance to the outcome what treatment these patients get at the scene of accident, during transportation to the hospital, during surgery and what kind of rehabilitation they get after the hospital stay. It may be that good treatment in one of these periods may be occluded by inadequate treatment in other treatment periods.
2) In Study 1 we used a stepwise prediction model and therefore did not adjust for the well-known prognostic factors age, GCS and pupil reactivity. According to the IMPACT studies, covariate adjustment should be pre-specified and include established strong predictors for outcome (Maas et al., 2013) and this was done in Study 2.
3) The IMPACT investigators also recommend not only to have one BP level (e.g. systolic BP < 90 mmHg) since also a supernormal systolic BP is associated with an unfavorable outcome (Maas et al., 2013). According to this argument we should probably also have had information of hypoglycemic episodes in addition to hyperglycemic episodes on both Study 1 and 2.
4) Even though we did register how many days the patients had episodes of recorded deviations from treatment goals (e.g. 29 patients in Study 1 had a Hgb < 8 g/dl for a

median time of 1 day (range 1-6 days)), we did not register if these days occurred in the acute phase after the trauma or later during the ICU stay, except for physiological deviations the first day after trauma. It is reasonable to think that severe deviations are more crucial if present during the acute phase than later when the cerebral condition has stabilized. In addition we did not study whether having deviations in variables for a longer duration, e.g. having several days with anemia, could be associated with a worse outcome than if the patient only had anemia for one day.

Strengths with the studies

1) By the time when Study 1 was published there were few studies focusing on ICU complications and deviations from the desired treatment in TBI patients. Even though it was a retrospective, single center study it contributed to an increased focus on this research subject.
2) By doing a prospective study (Study 2), the associations between deviations in treatment goals and outcome were more reliable than in the retrospective study.
3) Even though Study 3 included few patients we had many 2-hour interventions (52) and ICP measurements (674) that were analyzed. Stein et al. (2011) found that even transient elevations in ICP and transient decrements of CPP affected the outcome, and therefore emphasized the importance of frequent measurements.
4) There were few missing data in all the 3 studies.

5.5 Ethics

The aim of all the three studies was to focus on and to improve the treatment we give to patients who have suffered from a TBI and thereby help to improve their long-term outcome. The most important issue when doing observations and studies on all patients and especially in unconscious patients who cannot initially object, is to give the patients the best standard of care and act on behalf of the patients interests at all times. According to the principles of the Helsinki declaration this includes considering risks and benefits by participating in the studies. The patients who were included in our studies did not have any advantages in participating. On the other hand, by participating they were not exposed to additional risk since they were given standard care and no new therapy was introduced. Furthermore, adult patients who regained capacity to consent were given the opportunity to withdraw from participating. When performing Study 3 we were required to give information and receive a consent by the patient's next of kin early during the ICU stay for patients with a severe clinical condition. To avoid that the patients' next of kin should feel obliged to give their consent to participate in the study, the doctor involved in the study was not the doctor responsible for the treatment of the patient. In another study the main reason for giving consent to participate in a clinical study (on behalf of the patient) was to contribute to clinical research, whereas the second most common reason was that participating in the study might benefit the patient (van Stuijvenberg et al., 1998). One of the most common reasons for participating in our third study, as mentioned by the patients next of kin, was the opportunity to contribute to possible improvement of treatment in future TBI patients as long as it did not cause additional risk to the patient. They all gave consent and later none of the patients who regained capacity to consent withdrew from the study.

5.6 Suggestions for future research

Treatment of patients suffering from a traumatic brain injury starts at the scene of accident and continues at the hospital and during the rehabilitation phase and future research should focus on all these phases. However, performing studies involving patients in neurocritical care is challenging. Even though there have been a considerable amount of research in this field, an international, consensus conference reviewing studies to give recommendations on bedside physiologic monitoring only found a few studies with high quality of evidence (Le Roux et al., 2015).

Different ongoing and promising studies for future research in patients suffering from TBI are summarized in a review by Rosenfeld et al. (2012). They mention studies on new biomarkers and additional monitoring with cerebral oximetry and measuring cerebral blood flow. They also discuss possibilities of new drugs in TBI treatment such as erythropoietin and tranexamic acid as well as hormonal effects of progesterone. However, recent studies did not show any benefit of using erythropoietin and progesterone in TBI patients (Robertson et al., 2014, Skolnick et al., 2014). In addition, Rosenfeld et al. recommend the use of comparative effectiveness research (CER), comparing different treatment models and interventions given to TBI patients. Maas et al. (2012) also recommend the use of CER in TBI research. However, this would require including a large patient population, emphasizing the importance of developing large TBI datasets such as the IMPACT studies and the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) pilot data set (Yue et al., 2013). Another large TBI data set will be the ongoing Collaborative European Neuro Trauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. This is a prospective multicenter observational study of TBI patients in 22 countries in Europe and Israel (Maas et

al., 2015). The aim of this study is to better characterize brain injuries and to be able to individualize and improve treatment in TBI patients.

As mentioned by Le Roux et al. (2014) there are numbers of different variables that may have an effect on the course of the TBI patient but the most important issue is how we choose to handle all the given information. It also requires cooperation between different hospitals since one hospital cannot study and be experienced at using all different modalities in TBI treatment and monitoring. The International Initiative for Traumatic Brain Injury Research (InTBIR) is one platform for such cooperation (Menon and Maas, 2015, http://intbir.nih.gov (19.04.2016)). As stated by Manley and Maas (2013): “The complexity of TBI is such that no single investigator, institution, funding organization, or private company can make progress on its own.”

6. Conclusions

Study 1: Deviations in physiological variables are frequent during ICU and HDU treatment of patients suffering from severe traumatic brain injury. Pulmonary complications are frequent, with pneumonia being the most common extracranial complication during the ICU/HDU stay. During intensive care treatment, age, GCS, hypotension, elevated blood sugar and hypoalbuminemia can be associated with an unfavorable outcome.

Study 2: Deviations from specific treatment goals despite there being a treatment protocol of TBI patients are frequent. Pulmonary complications are common during the ICU/HDU stay, whereas other extracranial complications are rare. Age, GCS score, pupil dilation, ISS, ICP > 25 mmHg, elevated blood sugar and pneumonia are associated with a worse outcome.

Study 3: We did not observe any difference in ICP and $PaCO_2$ when comparing PC and PRVC ventilation in patients with a moderate or severe TBI. PRVC ventilation resulted in less fluctuations in both ICP and $PaCO_2$, but the magnitude of this difference is minor and probably not of any clinical importance.

Together, these articles contribute to give information concerning the treatment TBI patients receive in the ICU and emphasizes the importance of a goal directed treatment to improve and optimize the outcome in these patients.

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8. Papers 1-3

8.1 Errata

In paper 1, the title in reference nr 23 should be hypotension, not hypertension (Manley G, Knudson M, Morabito D et al. Hypotension, hypoxia, and head injury. Arch Surg 2001; 136: 1118–23).

In paper 1, the year of publication for reference nr 25 is 1977, not 1997 (Thomas DJ, Marshall J, Ross Russell W, Wetherley-Mein, Du Boulay GH, Pearson TC, Symon L, Zilkha E. Effect of haematocrit on cerebral blood-flow in man. Lancet 1977; 2: 941–3).

8.2 Copy right

Paper I

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Severe head injury: control of physiological variables, organ failure and complications in the intensive care unit

K. Schirmer-Mikalsen[1], A. Vik[2,4], S. E. Gisvold[1,5], T. Skandsen[3,4], H. Hynne[1] and P. Klepstad[1,5]
[1]*Department of Anaesthesia and Acute Medicine,* [2]*Department of Neurosurgery,* [3]*Department of Physical Medicine and Rehabilitation, St. Olav University Hospital,* [4]*Department of Neuroscience,* [5]*Department of Circulation and Medical Imaging, Medical Faculty, Norwegian University of Science and Technology, Trondheim, Norway*

Background: In patients with severe head injury, control of physiological variables is important to avoid intracranial hypertension and secondary injury to the brain. The aims of this retrospective study were to evaluate deviations of physiological variables and the incidence of extracranial complications in patients with severe head injury. We also studied if these deviations could be related to outcome.
Patients and methods: One hundred and thirty-three patients were included during a 5-year period (1998–2002). Deviations from treatment goals for the following physiological variables were studied: blood pressure, haemoglobin, blood sugar, serum sodium, serum albumin and temperature. Extra cerebral organ complications were also recorded as well as outcome at 6 months.
Results: The median age was 32 years (range; 1–88 years). Median Glasgow Coma Scale (GCS) before intubation was 6 (range; 3–14). The frequencies of severe deviations from the desired values of the physiological variables for at least one treatment day were: hypotensive episodes (systolic BP < 90 mmHg) – 20%, anaemia (hgb $<$ 8 g/dL) – 22%, blood glucose >10 mmol/l – 26%, serum sodium concentration <130 mmol/l – 10%, serum albumin <25 g/l^{-1} – 31% and hyperthermia >39 °C – 24%. Pneumonia was diagnosed in 71% and Acute Lung Injury (ALI)/Adult Respiratory Distress Syndrome (ARDS) in 26% of the patients. Other complications such as severe sepsis (6%), renal failure (1.5%), a coagulation disorder (6%) and liver failure (one patient) were infrequent. Age, GCS, hypotension during the first day of treatment, elevated blood sugar and low albumin predicted an unfavourable outcome.
Conclusions: Deviations of key physiological variables and pulmonary complications were frequent in patients suffering from severe head injury. During intensive care treatment, hypotension, elevated blood sugar and hypoalbuminemia are possible independent predictors of an unfavourable outcome.

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Key words: Severe head injury; secondary brain injury; control of physiological variables; intensive care; outcome; pneumonia.

Guidelines recommend stabilization of patients with severe head injury within specified treatment goals related to oxygenation, ventilation, blood pressure, temperature, blood sugar, serum sodium and albumin to avoid secondary brain damage and development of intracranial hypertension (1–6). However, strict compliance to the treatment goals may be difficult to achieve in day-to-day practice in the intensive care unit (ICU). Potential causes for physiological deviations are other intercurrent conditions such as respiratory failure, sepsis or heart failure, lack of education, lack of vigilance, insufficient staffing or other organizational issues. It is not known to what extent physiological variables differ from defined treatment goals during day-to-day practice in the ICU. Furthermore, although many studies evaluate the effect of elevated intracranial pressure or reduced cerebral perfusion pressure on outcome (2, 7–9), the consequences of deviations from other physiological variables have not been studied in detail.

Thus, the aims of this study were to evaluate the frequency of deviations in physiological variables and risk of extracranial complications in patients with severe head injuries during treatment in the ICU and high-dependency unit (HDU). We also wanted to explore the relationship of such deviations and complications to outcome.

Material and methods

The study was done in accordance with the principles of the Helsinki declaration. The Regional Committee for Medical Research Ethics, Health Region IV,

Norway, approved the study. All 146 patients with severe head injury admitted to our hospital during a 5-year period (1998–2002) were retrospectively reviewed. The hospital is the sole neurosurgical facility in a health care region of about 660,000 inhabitants resulting in a total of 25–30 patients presenting with severe head trauma each year. Patients were included if the Glasgow Coma Scale (GCS) was $\leq$8 before or after hospital admission. Also, patients with a GCS $>$8 before intubation were included if they deteriorated. All had intracranial traumatic pathology on computer tomography (CT). Patients for whom treatment was withheld at the time of admission as a result of severe head injury with no hope for survival ($n = 9$), and patients who died from causes not related to the head injury within the first 24 h ($n = 2$) were excluded. Furthermore, another two patients were excluded from the analyses as a result of a lack of sufficient medical records or no stay in the ICU/HDU. Thus, 133 patients fulfilled the inclusion criteria.

Treatment goals (Table 1)

During the study period, the hospital followed the European Brain Injury Consortium (EBIC) guidelines for treatment of severe head injury (1) (Table 1). However, at the time the hospital did not have a specific step-by-step guideline describing how to reach these treatment goals.

The patients were intubated and received controlled ventilation. Sedation was achieved by a combination of continuously infused intravenous (i.v.) midazolam and morphine. Propofol was used for some patients during weaning from the ventilator. For hypotension or failure to reach the target cerebral perfusion pressure (CPP), circulatory support was provided with colloids and crystalloids with additional vasoactive agents (dopamine or norepinephrine) as required. The patients were not routinely given a continuous infusion of insulin for regulation of blood glucose. The desired blood glucose level was $<$ 8 mmol/l. The intracranial pressure (ICP) was measured either using an intraparenchymal or an intraventricular pressure device. The target CPP was usually set at 60–70 mmHg. Increases in ICP (ICP above 20 mmHg) were treated with sedation and analgesia, moderate hyperventilation ($PaCO_2$ 4–4.5), osmotic therapy (mannitol and/or hypertonic saline) and cerebrospinal fluid (CSF) drainage. Patients with increased ICP not responsive to standard treatment were administered more extensive hyperventilation, continuous infusion of thiopental, and in some cases corticosteroids or mild hypothermia. Corticosteroids are not recommended in EBIC guidelines, and are no longer a treatment for intracranial hypertension at our department. Muscle relaxants were only used occasionally. Decompressive craniectomies were not performed in the treatment of head injured patients during this time period, although the bone flap was not replaced during the neurosurgical operation in some patients.

Deviation from treatment goals: definitions/criterions

The frequencies of physiological observations not within the recommended limits were identified by reviewing all charts completed during the patients stay in the ICU/HDU. The observed values and number of daily observations corresponding to a moderate or severe deviation from the treatment goals were defined as shown in Table 2. Patients were identified as cases if having observations defined as outside the target values for at least one day. Some patients had observations corresponding to moderate or severe deviations during separate days and were therefore registered as both moderate and severe deviation cases.

Blood gas analyses, including the measurement of haemoglobin, blood glucose and electrolyte serum

Table 1

Treatment goals in the intensive care unit (ICU)/high-dependency unit (HDU).

	Parameters	According to EBIC
(1) Ventilation	Saturation of oxygen (SaO_2)	$>$95%
	Arterial partial pressure of oxygen (PaO_2)	$\geq$13 kPa (100 mmHg)
	Arterial partial pressure of carbon dioxide ($PaCO_2$)	4–4.5 kPa (30–35 mmHg)
(2) Blood pressure	Mean arterial blood pressure (MAP)	$\geq$90 mmHg (adults)
(3) Intracranial measures	Intracranial pressure (ICP)	$\leq$20–25 mmHg (adults)
	Cerebral perfusion pressure (CPP = MAP-ICP)	$>$60–70 mmHg
(4) Blood glucose	Avoid hyperglycaemia	No exact blood sugar limit
(5) Body temperature	Avoid hyperthermia	No exact limit mentioned
(6) Serum Sodium	Avoid hyponatremia	No exact limit mentioned

EBIC, European Brain Injury Consortium.

Table 2

Deviation from treatment goals.

	Moderate/severe deviations	
Respiratory	$PaCO_2$ 5–6/ >6 kPa, PaO_2 8–11/ <8 kPa	Moderate/severe deviations if registered at ≥3 observations/day
Circulatory	Adult systolic blood pressure <90 mmHg	Registered as a deviation if measured at ≥3 times/day
Haemoglobin (Hgb)	8–10/ <8 g/dl	Moderate/severe deviations if registered once during the same day
Blood glucose	8–10/ >10 mmol/l	Moderate/severe deviations if registered ≥3 times/day
Serum sodium	130–135/ <130 mmol/l	Moderate/severe deviations if registered ≥3 times/day
Serum albumin	<25 g/l	Measured any time during the ICU/HDU stay
Temperature	38–39/ >39 °C	Moderate/severe deviations if registered ≥3 times/day

ICU, intensive care unit; HDU, high-dependency unit.

concentration, were usually taken 5–10 times daily in the ICU, although less frequently in the HDU as the patients were usually more stable during this phase. The patients' blood pressure was observed continuously and registered hourly in the ICU and at the time of hypo- or hypertensive episodes, although again less often in the HDU. ICP was registered hourly in both the ICU and the HDU and at the time of ICP increases.

Organ failure during ICU/HDU treatment

The incidence of organ failure and major intercurrent conditions were identified by reviewing the patients' records, charts and radiologist consultants' evaluation of X-rays (KSM). Respiratory and circulatory complications such as ventilator-associated pneumonia (VAP), acute lung injury (ALI), adult respiratory distress syndrome (ARDS) and severe sepsis were identified. The definitions for each organ failure or intercurrent conditions are given in Table 3. Using the sequential organ failure assessment score, renal failure, liver failure and a coagulation disorder were defined at values corresponding to three or more (10).

Outcome

A specialist in physical medicine and rehabilitation not involved in the acute care of the patients collected the 6-months Glasgow Outcome Scale (GOS) retrospectively (TS). GOS 5 and 4 represented good recovery and moderate disability, while 3, 2 and 1 represented severe disability, a persistent vegetative state and death. The patients' outcomes were dichotomized into favourable (GOS 5 and 4) and unfavourable (GOS 3, 2 and 1).

Statistics

The results are given as numbers, percentages, median and ranges as appropriate. Pearson's chi-square test was used when comparing proportions. In the explorative analyses for the relationship between observations outside the standard treatment goals and GOS outcome, multiple logistic regression analyses were used. The independent variables were age, GCS, hypotension (systolic BP <90 mmHg), hypoventilation (pCO_2 >6 kPa), hypoxia (PaO_2 <8 kPa), anaemia (Hgb <8 g/dl), hyperglycaemia (blood glucose >10 mmol/l), hyponatremia (serum sodium <130

Table 3

Definition of extra cerebral organ complications.

Complication	Definition
Ventilator-associated pneumonia (VAP)	Artificial ventilation >48 h, infiltrates on chest X-ray, leucocytes >10 or <3, temp. >38.5 °C or <35 °C and purulent tracheal secretions
Pneumonia (other than VAP)	As above but start of symptoms before 48 h of respiratory treatment
Acute lung injury (ALI)	Acute respiratory failure, PaO_2/FiO_2 ratio <39.9 kPa, bilateral infiltrates on chest X-ray and no signs of heart failure
Adult respiratory distress syndrome (ARDS)	Acute respiratory failure, PaO_2/FiO_2 ratio <26.6 kPa, bilateral infiltrates on chest X-ray and no signs of heart failure
Severe sepsis	Sepsis with organ dysfunction, hypo perfusion or hypotension in spite of adequate fluid therapy
Renal failure	Serum creatinine >299 μmol/l or diuresis less than 500 ml/24 h (adults)
Bleeding disorder	Platelets $<50 \times 10^9$/l
Liver failure	Serum bilirubin >101 μmol/l

mmol/l), hypoalbuminia (serum albumin <25 g/l) and hyperthermia (central body temperature >39 °C). For all the physiological variables, patients were defined as cases (one or more days with deviations) vs. non-cases. In addition, a similar analysis was performed using only deviation in physiological variables observed at the first day of hospitalization. In the multiple regression analyses, a backward stepwise method was used applying a significance level of 0.05 for significance and a probability for removal of 0.10.

Results

Demographics

The 133 patients which were included consisted of 108 men and 25 women with a median age of 32 years (range; 1–88 years). The majority of head injuries were caused by either traffic (50%) or a fall-related accident (35%). Median GCS before intubation was 6 (range; 3–14, missing: 13). The 13 patients with missing GCS were all reported as comatose, but the exact GCS was not available. Median Simplified Acute Physiology Score II in patients >18 years with severe head injury who were treated at the ICU ($n = 112$) was 43 (range; 14–80, missing 2).

About half of the patients (48%) had other serious injuries. Trauma to the chest was most common (29%), followed by facial trauma (21%) and fractures/lacerations to the extremities (20%). One hundred and thirty-one of the 133 patients received ventilatory support in the ICU/HDU. The most frequent cerebral CT diagnoses were contusions (72%), a subdural haematoma (55%) and a subarachnoid haemorrhage (56%). Most patients received ICP monitoring (84%) and 48% were operated on for an intracranial mass lesion. Nineteen patients died of intracranial hypertension. The median total length of stay (LOS), including both the ICU and the HDU stay, was 12 days (range; 0.5–49 days). The median LOS in the ICU and the HDU was 7 and 6 days, respectively.

Key physiological variables, organ failures and complications

Hypotensive episodes (systolic BP <90 mmHg) were registered in 20% of the adult patients (Table 4). Forty-eight per cent of the patients who died of their head injury during the first 6 months after the trauma had hypotensive episodes during their ICU/HDU stay, compared with 18% in the survival group ($P < 0.001$). Severe anaemia occurred in 22%. Twenty-six per cent had elevated blood glucose (>10 mmol/l), and 46% of the patients with blood glucose more than 10 mmol/l died within 6 months after the trauma. Ten per cent of the patients had serum sodium <130 mmol/l. Serum albumin was <25 g/l in 31% of the patients. Despite that one of the treatment goals was to avoid elevated body temperature, 24% had episodes of a body temperature of more than 39 °C.

Pneumonia was a common complication (Table 5). Most frequent was VAP diagnosed in 49% of the patients. Of the 47 patients who got continuously infusion with barbiturates during some part of their intensive care, as many as 81% got pneumonia during their ICU/HDU stay compared with 67%

Table 4

Recorded deviations from treatment goals.

		Number of patients ($n = 133$)	Days median (range)	Patient data missing*
Respiration	$PaCO_2$ 5–6 kPa	94 (71%)	3 (1–22)	5
	$PaCO_2$ >6 kPa	33 (25%)	2 (1–16)	4
	PaO_2 8–11 kPa	91 (68%)	4 (1–20)	5
	PaO_2 <8 kPa	13 (10%)	1 (1–3)	3
Circulation	Systolic BP <90 mmHg (adults)	26 (20%)	1 (1–8)	3
Haemoglobin	Hgb 8–10 g/dl	107 (80%)	6 (1–38)	3
	Hgb <8 g/dl	29 (22%)	1 (1–6)	2
Blood glucose	Blood glucose 8–10 mmol/l	69 (52%)	2 (1–9)	7
	Blood glucose >10 mmol/l	35 (26%)	1 (1–6)	6
Serum sodium	Serum sodium 130–135 mmol/l	62 (47%)	3 (1–12)	3
	Serum sodium <130 mmol/l	14 (10%)	2 (1–3)	1
Serum albumin	Serum albumin <25 g/l	41 (31%)	2 (1–24)	21
Temperature	Temperature 38–39°C	96 (72%)	4 (1–28)	6
	Temperature >39°C	32 (24%)	2 (1–18)	1

Some patients had both severe and moderate deviations and are therefore counted twice.
*Missing data as a result of insufficient/lacking chart for one or more days.

Table 5

Extra cerebral organ complications during the intensive care unit (ICU)/high-dependency unit (HDU) stay.

Complications	Number of patients ($n = 133$)	Patient data missing
Ventilator-associated pneumonia (VAP)	65 (49%)	1
Pneumonia (other than VAP)	33 (25%)	1
Acute lung injury (ALI)	34 (26%)	0
Adult respiratory distress syndrome (ARDS)	30 (23%)	0
Serious sepsis	8 (6%)	1
Septic shock	0	0
Renal failure	2 (1.5%)	0
Bleeding disorder	8 (6%)	0
Liver failure	1 (0.8%)	0

of the rest of the patients. The difference was, however, not significant ($P = 0.181$). ALI or ARDS occurred in 26% of the patients. One-third of the hypoventilated patients had episodes of $PaCO_2$ values above 6 kPa (Table 4). Other extracranial complications such as severe sepsis septic shock, renal failure, coagulation disorder and liver failure were infrequent (Table 5).

Outcome

The 6-months GOS showed a favourable outcome (GOS 4 and 5) in 37% ($n = 49$) of the patients, while 59% ($n = 78$) had an unfavourable outcome (GOS 1–3) (missing GOS: 6 patients). For GOS 6 months after the injury, age ($P = 0.013$) and blood sugar deviations ($P = 0.044$) during treatment were predictors of an unfavourable outcome. When analysing the relationship between the first day of ICU/HDU treatment and GOS at 6 months, GCS ($P = 0.020$) and hypotension ($P = 0.022$) predicted an unfavourable outcome. The in-hospital mortality was 18% (24 patients) while 6-months mortality was 25% (33 patients). Predictors of mortality were age ($P = 0.012$), GCS ($P = 0.015$), hypotension ($P = 0.007$), and hypoalbuminemia ($P = 0.036$). The corresponding predictors when analysing for observations at day 1 during the ICU/HDU stay were age ($P = 0.031$), high blood sugar ($P = 0.002$) and hypoalbuminemia ($P = 0.046$).

Discussion

The key finding in our investigation of patients with severe head injury was that important physiological parameters frequently deviated from the treatment goal during intensive care. Furthermore, in patients with severe head injury, pulmonary complications occurred frequently, whereas other extracranial organ failures were infrequent. These factors seemed to contribute significantly to the final outcome of the patients.

The mechanisms causing extracranial complications are complex involving infections, traumatic injuries in other organs, inflammatory mediators, hormonal changes and disturbed vasomotor control (11, 12). The high incidence of pneumonia including VAP found in our study (Table 5) corresponds with the high incidence found in a prospective investigation from Bronchard et al. (13) and data from the Traumatic Coma Data Bank (12), but it is higher than observed by others (4, 14). In patients included in the Traumatic Coma Data Bank, pulmonary infections were a significant independent predictor of an unfavourable outcome. In contrast, Polderman et al. (4) only registered pulmonary complications (infections, pneumothorax and bleeding) in 11% of the patients.

While the findings of Stover and Stocker (15) conclude that a barbiturate coma in patients with traumatic brain injury may cause reversible leucopenia and an increased infection rate, we could not find a significant difference in the incidence of pneumonia in this group of patients.

It is well known that there is a correlation between respiratory dysfunction and mortality (11, 16). Earlier reports (2) have described an increase in the risk of ARDS when the lower CPP threshold was set at 70 mmHg, compared with a threshold of 50 mmHg. Which value is an adequate cerebral perfusion pressure is controversial (8, 9). While the EBIC guidelines have been recommending a CPP threshold of 60–70 mmHg as was used in our study, the Lund concept (17–22) argues for a lower CPP limit (down to 50 mmHg in adults).

In the analyses of outcome, hypotension during the first day of stay in the ICU independently predicted an unfavourable outcome after 6 months in our study. Earlier studies have shown that even brief

periods of mild hypotension adversely affects outcome in patients with severe traumatic brain injury (3, 12, 14, 23, 24). However, it has been argued that hypotension is most critical during the initial phase after the injury, i.e. before arriving at the ICU (18), but the negative consequences of hypotension in these patients later during the ICU stay are well documented (3, 10, 12).

Many of our patients had a Hgb level <10 g/dl, but we did not observe any relationship between anaemia and outcome. It may be speculated that lower viscosity as a result of anaemia improves microcirculation in parts of the brain that are at risk (25, 26). Proponents of the Lund therapy (17), however, advocate blood transfusions if needed, to maintain a Hgb level above 11 g/dl in order to improve oxygen transport to the injured brain (27). Thus, there may be both detrimental and beneficial effects from anaemia.

Almost half of the patients with blood glucose of more than 10 mmol/l died within 6 months after severe head injury in our study, and in the multiple regression analyses elevated blood glucose was an independent predictor of outcome. This is in agreement with other studies (5, 24, 28, 29).

In a systematic review, Haynes et al. showed that albumin treatment gave reduced mortality, disability and neurological deficits in patients with brain injury (30). While the Lund concept includes albumin infusion in their guideline for maintaining colloid osmotic pressure, it is not a routine treatment in most ICUs including our ICU/HDU. Experts who do not advocate albumin claim that it is the total osmolality of the blood that is important for the fluid shifts over the blood–brain barrier. Because albumin contributes little to the total osmolality compared with serum sodium, the effects from administrating albumin infusions are believed to be limited (31, 32). However, for the patients included in the present study, low albumin serum concentrations were associated with an increased risk of death. This is in agreement with more recent research showing that albumin reduces cerebral oedema and has a neuroprotective effect (6, 33–35).

The low frequencies of severe sepsis, renal failure and liver failure found in our patients are also described in previous studies (2, 4, 12, 14, 36). However, several studies (12, 37, 38) found a higher incidence of coagulopathy than observed in this study. Our data suggest that in patients with severe head injury, organ failures other than those of respiratory and circulatory origin seldom contribute to an unfavourable outcome. However, our finding may be as a result of a low number of patients that fail to elucidate the consequences of infrequent complications. This speculation is supported by the fact that the Traumatic Coma Data Bank (12) has shown that extracranial complications such as coagulopathy and sepsis are also significant predictors of a less favourable outcome.

In the present study, the overall incidence of extracerebral organ failure agrees with a recent paper by Zygun et al. (36). Zygun et al. also observed that the development of non-neurological organ dysfunction was associated with worse outcome independent of age and GCS. These observations call for close attention to details in the intensive care treatment of patients with severe head injury. Protocol-driven treatment offers a significant benefit, both generally and in head-injured patients (39, 40). In our study and the study by Zygun et al., it is not investigated if changes in key physiological parameters were unavoidable results from other injuries, organ failures or altered central nervous autonomic regulation or as a result of a lack of attention to detail during treatment.

We recognize several limitations in this study. First, because of the retrospective design, some data are missing. Second, beyond the separate assessment of the first day of hospitalization, we have not differentiated between the acute phase in the ICU and the more subacute period in the HDU. It is reasonable to believe that deviations are more crucial if present during the acute phase of head injury treatment.

Conclusion

This study demonstrates that undesired and potentially harmful changes in physiological variables are frequent during ICU and HDU treatment of patients suffering from severe head injury. Pulmonary complications are also frequent, with pneumonia being the most common problem. During intensive care treatment, age, GCS, hypotension, elevated blood sugar and hypoalbuminemia are possible independent predictors of an unfavourable outcome.

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Address:
Kari Schirmer-Mikalsen
Department of Anaesthesia and Acute Medicine
St. Olav University Hospital
Trondheim
Norway
e-mail: kari.schirmer@stolav.no

Paper II

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Intensive care and traumatic brain injury after the introduction of a treatment protocol: a prospective study

K. Schirmer-Mikalsen[1], K. G. Moen[2,3], T. Skandsen[3,4], A. Vik[2,3]* and P. Klepstad[1,5]*
[1]*Department of Anaesthesia and Acute Medicine, St.Olav University Hospital, Trondheim, Norway,* [2]*Department of Neurosurgery, St.Olav University Hospital, Trondheim, Norway,* [3]*Department of Neuroscience, Medical Faculty, Norwegian University of Science and Technology, Trondheim, Norway,* [4]*Department of Physical Medicine and Rehabilitation, St.Olav University Hospital, Trondheim, Norway and* [5]*Department of Circulation and Medical Imaging, Medical Faculty, Norwegian University of Science and Technology, Trondheim, Norway*

Background: Traumatic brain injury (TBI) treatment protocols have been introduced in the intensive care unit (ICU) to avoid secondary brain injury. In this study, we aimed to evaluate the deviations from such a treatment protocol and the frequency of extracranial complications, and relate these findings to outcome.
Methods: During a 5-year period (2004–2009), 133 patients with severe TBI [Glasgow Coma Scale (GCS) score ≤ 8] were prospectively included. The following deviations from treatment goals were studied: intracranial pressure (ICP), blood pressure, haemoglobin, blood glucose, serum sodium, serum albumin, body temperature and extracranial complications during the ICU stay. Outcome was assessed using Glasgow Outcome Scale Extended score at 12 months.
Results: The frequencies of deviations from the treatment goals were: episodes of intracranial hypertension 69.5% (of monitored patients), hypotension 20.3%, anaemia 77.4%, hyperglycaemia 42.9%, hyponatremia 34.6%, hypoalbuminemia 30.8% and hyperthermia 54.9%. Pulmonary complications were common (pneumonia 72.2%, acute respiratory distress syndrome/acute lung injury 31.6%). Thrombocytopenia (4.5%), severe sepsis (3.0%), renal failure (0.8%) and liver failure (0.8%) were infrequent. Twenty-six (19.5%) patients died within the first 12 months due to the head injury. Age, GCS score, pupil dilation, Injury Severity Score (ISS), ICP > 25 mmHg, hyperglycaemia and pneumonia predicted a worse outcome.
Conclusions: Deviations from the TBI treatment protocol were frequent. Pneumonia was the most frequent extracranial complication. Age, GCS score, pupil dilation, ISS, high ICP, hyperglycaemia and pneumonia predicted a worse outcome.

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Hospital treatment of patients with traumatic brain injury (TBI) is initially directed at limiting the extent of secondary brain injury. Neuroprotective therapy includes multiple interventions, both surgically and medically, involves health care workers from several professions and has to be delivered continuously. Consequently, detailed treatment protocols for TBI patients have been developed for the various stages of the TBI trajectory including treatment within the intensive care unit (ICU).

Before the introduction of a specific TBI treatment protocol, the treatment policy in our ICU and high dependency unit (HDU) for patients with severe TBI was based on the European Brain Injury Consortium (EBIC) guidelines.[1] Although we had a written procedure, it was not very accurate and did not contain specific information about what treatment should be given highest priority. In a retrospective study of patients with severe TBI admitted to our hospital during the years 1998–2002, we showed that deviations from the proposed treatment targets in the EBIC guidelines were frequent.[2] Furthermore, in this study, hypotension, elevated blood glucose and hypoalbuminemia predicted an unfavourable outcome, suggesting that the failure to achieve defined ICU treatment targets could have long-term clinical consequences.[2]

In 2003, we introduced a three-level treatment protocol based on the EBIC guidelines to avoid secondary brain injury and intracranial hypertension in TBI patients. This protocol was implemented in the

*These authors contributed equally to the work.
The work was carried out at St Olav University Hospital in Trondheim, Norway.

hospital quality assurance system, and the content was disseminated by education and always available at each patient's bed and thereby reducing the risk of discontinued treatment after duty shift handovers. Previous studies that compare the outcomes in TBI patients before and after an introduction of a TBI treatment protocol generally find that the introduction of a detailed treatment protocol improves care.[3–5] However, these studies do not report detailed information in numbers of deviations from the agreed treatment goals.

Thus, the aim of this study was to prospectively evaluate the frequency of deviations from defined protocol treatment goals and the frequency of extracranial complications during the ICU stay after the introduction of a TBI treatment protocol. We also wanted to study if such deviations and complications could predict outcome.

Material and methods

Patients and setting

The study was conducted at St Olav University Hospital, a tertiary referral centre for all neurosurgical activities serving a population of about 680,000. All patients with a severe TBI admitted to the hospital ($n = 161$) were prospectively screened during a 5-year period (from 15 October 2004 until 16 October 2009). Patients were included if Glasgow Coma Scale (GCS) score was ≤ 8 before or after hospital admission. Patients with low GCS score due to intoxication were not included. Patients were also excluded if no active therapy was initiated after admission either due to a head injury appraised to have no hope of survival ($n = 12$) or if ICU therapy was not initiated due to high age and/or other concomitant severe chronic diseases ($n = 6$). Also, patients who died because of extracranial injuries within the first 24 h after admission ($n = 6$) were excluded. Three patients did not consent to follow up, and finally, one patient was a foreigner and was lost to follow up. Thus, 133 patients were finally included in the study.

The treatment protocol

The protocol includes three treatment levels where level 1 is the basic intensive TBI treatment (Table 1). The patients receive adequate sedation and analgesia, and if required intubation and mechanical ventilation. Intracranial haematomas are surgically evacuated if indicated. Sedation is administered using continuously infusions of intravenous midazolam and morphine. Some patients are given propofol for shorter periods during ventilator weaning. The upper body is elevated 15–20 degrees. To maintain the desired blood glucose level (4.5–6.5 mmol/l), a continuous infusion of insulin is established if needed. At haemoglobin < 100 g/l, blood transfusions are given. Hyponatremia (< 140 mmol/l) is treated with isotonic NaCl solutions or hypertonic saline.

ICP was measured either by using an intraparenchymal or an intraventricular pressure device. The zero level for ICP measurements when using a ventricular drainage was at the level of the external auditory meatus and the zero level of the arterial pressure was by the level of the heart. Elevated ICP above 20 mmHg (> 15 mmHg in children < 1 year old) was initially treated with increased sedation and boluses of thiopental (level 1). Crystalloids and vasoactive agents (dopamine or norepinephrine) were administered to maintain desired cerebral perfusion pressure (CPP). The protocol was changed in 2006 when the target CPP was reduced from 70 mmHg to 60 mmHg in adults and it was introduced paediatric age-specific CPP targets (45–60 mmHg in children depending on the child's age).

If still not satisfactory ICP levels after completion of level 1 treatment alternatives, more intensive treatment is required. In level 2, osmotic therapies (mannitol and/or hypertonic saline), cerebrospinal fluid (CSF) drainage, moderate hyperventilation ($PaCO_2$ 4–4.5 kPa) and moderate hypothermia (35–36°C) are administered. If the patients continue to have elevated ICP and low CPP, despite level 2 treatment, they are operated with decompressive craniectomia (level 3) or other treatments such as continuous infusion of thiopental, extensive hyperventilation ($PaCO_2$ 3.6–4.0 kPa), hypothermia (< 35°C) and lumbal CSF drainage. In a modified version of the treatment protocol in 2006, decompressive craniectomy was indicated as the first priority in level 3, and from 2008, therapeutic hypothermia was no longer given to children.[6–8] If not an ICP measurement device was placed, the patients were treated according to TBI protocol level 1.

Deviations from treatment goals: definitions/criteria

The data were registered by an intensive care nurse and were quality checked by a specialist in anaesthesiology (K. S-M.). Simplified acute physiology score II (SAPS II) was calculated for the first 24 h.[9] The Injury Severity Score (ISS) was registered according to Baker et al.[10] The frequencies of physi-

Table 1

TBI treatment protocol for the 133 patients included.

Level	Treatment	Definitions		Frequency % ($n = 133$)
1	Adequate sedation and analgesia			
	Thiopental bolus	During procedures		49.6%
	15–20° elevation of the head			
	Surgical evacuation of haematoma if indicated			
	$PaO_2 > 13$ kPa or oxygen saturation > 95%			
	$PaCO_2$	Around 4.5 kPa		
	Haemoglobin (Hgb)	> 100 and < 120 g/l		
	Normovolemia			
	Normothermia	Temp. ≤ 37°C		
	Serum sodium	≥ 140 mmol/l		
	Serum glucose	4.5–6.5 mmol/l*		
	Cerebral perfusion pressure (CPP)**	Adult	≥ 60 mmHg	
		Children	> 45–60 mmHg, depending on age	
2	Check level 1!			
	Consider a new CT scan.			
	Hypertonic saline 2,9% (S-Na < 150 mmol/l)	Adult	250 ml	50.4%
		Children	1–2.5 mmol/kg,	
		If infusion	0.05–0.5 mmol/kg/h	
	Mannitol 150 mg/ml (S-Osm ≤ 320 mosm/kg)	Adult	200–300 ml	33.8%
		Children	0.25–1 g/kg	
	CSF drainage if possible			
	Moderate hyperventilation	$PaCO_2$	4.0–4.5 kPa	33.1%
	Moderate hypothermia (not in children)	Temp	35–36°C	26.3%
3	Check level 1 and 2!			
	Consider a new CT scan.			
	Decompressive craniectomy (high priority)			6.0%
	Barbiturate coma	Thiopental	1–5 mg/kg/h	11.3%
	Hyperventilation	$PaCO_2$	3.6–4.0 kPa	
	Hypothermia (not in children)	Temp < 35°C		14.3%
	Lumbal catheter for CSF drainage			6.8%

*The desired S-Glu level was changed to 4.5–8 mmol/l after the study period.
**Zero level of the arterial pressure is by the level of the heart. CSF, cerebrospinal fluid; CT, computer tomography.

ological values not within the recommended limits were identified by reviewing all ICU charts. Moderate or severe deviations from treatment goals were defined in Table 2. Blood gas analyses, including the measurements of haemoglobin, blood glucose and electrolytes serum concentration, were usually taken 5–10 times daily depending on the patient's clinical condition. Continuous intra-arterial blood pressure measurements and other vital parameters were documented hourly or as required. ICP was registered hourly and at the time of ICP increases. A moderate/severe deviation in ICP and CPP was defined as ICP 21–25 mmHg/ > 25 mmHg and CPP 50–59 mmHg/ < 50 mmHg, respectively. For both these variables, a deviation was registered if measured ≥ 3 times/day. However, if treatment was terminated due to no hope of survival, vital parameters including ICP after cessation of active treatment were not registered in the database.

Organ failure during ICU/HDU treatment

The definitions of extracranial complications are given in Table 3. The incidence of organ failure was identified by reviewing the patients' records, charts and radiologist consultants' evaluation of X-rays, computer tomography (CT) and magnetic resonance imaging (MRI). Complications such as ventilator-associated pneumonia (VAP), pneumonia due to other causes, acute lung injury (ALI), acute respiratory distress syndrome (ARDS) and severe sepsis were noted.[11,12] A sequential organ failure assessment (SOFA) score of three or four was used to define renal failure, liver failure and a coagulation disorder.[13]

Outcome assessment

A specialist in physical medicine and rehabilitation (T. S.) and a research nurse collected the 12-month Glasgow Outcome Scale Extended (GOSE) score.[14] GOSE score was not possible to score in the following cases: (1) patients who died of other causes than the head injury during the follow-up ($n = 1$), (2) patients who needed special care before the TBI ($n = 3$), (3) patients who got another injury during the follow-up study ($n = 1$) and (4) patients who were lost to follow-up ($n = 1$). Of the six patients

Table 2

Recorded deviations from treatment goals.

	Moderate/severe deviations*	Number of patients ($n = 133$)	Days median (range)	Patient data missing**
Respiration	$PaCO_2$ 5–6 kPa/	99 (74.4%)	3 (1–15)	6
	$PaCO_2 > 6$ kPa	21 (15.8%)	1 (1–9)	6
	PaO_2 8–11 kPa/	86 (64.7%)	3 (1–16)	6
	$PaO_2 < 8$ kPa	4 (3.0%)	1 (1-1)	6
Circulation	Systolic BP < 90 mmHg	27 (20.3%)	1 (1–10)	5
Haemoglobin (Hgb)	Hgb 80–100 g/l	101 (75.9%)	6 (1–27)	0
	Hgb < 80 g/l	22 (16.5%)	1 (1–19)	0
Blood glucose (S-Glu)	S-Glu 8–10 mmol/l/	52 (39.1%)	1 (1–4)	3
	S-Glu > 10 mmol/l	12 (9.0%)	1 (1–3)	3
Serum sodium (S-Na)	S-Na 130–135 mmol/l/	46 (34.6%)	2 (1–11)	0
	S-Na < 130 mmol/l	4 (3.0%)	1,5 (1–4)	1
Serum albumin	Serum albumin < 25 g/l	41 (30.8%)		12
Temperature (T)	T 38–39°C/	72 (54.1%)	3 (1–14)	2
	T > 39°C	21 (15.8%)	2 (1–9)	2

Some patients had both severe and moderate deviations and are therefore counted twice.
*$PaCO_2$, PaO_2, systolic BP, S-Glu, S-Na and T are registered as a moderate/severe deviation if deviations are measured ≥ 3 times/day. Hgb is registered as a moderate/severe deviation if deviation is measured once during the same day, while S-Alb is registered as a deviation if measured low any time during the ICU stay.
**Missing data as a result of insufficient/lacking chart for one or more days.

Table 3

Definition and frequencies of extracranial organ complications.

Complication	Definition	Frequencies (%)	Patient data missing*
Ventilator-associated pneumonia (VAP)	Artificial ventilation > 48 h, infiltrates on chest X-ray, leucocytes > 10 or < 3×10^9/l, temp. > 38.5°C or < 35°C and purulent tracheal secretions	47 (35.3%)	0
Pneumonia (other than VAP)	As above but start of symptoms before 48 h of respiratory treatment	50 (37.6%)	0
Acute lung injury (ALI)	Acute respiratory failure, PaO_2/FiO_2 ratio < 39.9 kPa, bilateral infiltrates on chest X-ray and no signs of heart failure	19 (14.3%)	1
Acute respiratory distress syndrome (ARDS)	Acute respiratory failure, PaO_2/FiO_2 ratio < 26.6 kPa, bilateral infiltrates on chest X-ray and no signs of heart failure	23 (17.3%)	1
Severe sepsis	Sepsis with organ dysfunction, hypoperfusion or hypotension in spite of adequate fluid therapy	4 (3.0%)	0
Renal failure	Serum creatinine > 299 μmol/l or diuresis less than 500 ml/24 h (adults)	1 (0.8%)	0
Bleeding disorder	Platelets < 50×10^9/l	6 (4.5%)	2
Liver failure	Serum bilirubin > 101 μmol/l	1 (0.8%)	3

*Missing data as a result of insufficient/lacking chart for one or more days.

where 12-month GOSE was not possible to score, three had a valid registered 6-month GOSE score, which was used in the analyses.

Statistical analyses

The descriptive data are given in numbers, percentages, median and ranges as appropriate. We used ordinal logistic regressions to explore the association between outcome and prognostic factors. Outcome was assessed by GOSE score as dependent variable. The GOSE scale was reclassified into worse outcome [GOSE score 1–4 (1 dead, 2–4 severe disability)], moderate disability (GOSE score 5–6) and good recovery (GOSE score 7–8), and the latter was chosen as reference category.

The following predictor variables were explored using univariable logistic regression: age (continuous variable), GCS score, pupil dilation during the first 24 h, hypotension (systolic BP < 90 mmHg), elevated ICP (21–25 mmHg and ICP > 25 mmHg), hypoventilation ($pCO_2 \geq 5$ kPa), hypoxia ($PaO_2 \leq 11$ kPa), anaemia (Hgb ≤ 100 g/l), hyperglycaemia (blood glucose ≥ 8 mmol/l), hyponatremia (serum sodium ≤ 135 mmol/l), hypoalbuminemia (serum albumin < 25 g/l), hyperthermia (central body temperature ≥ 38°C), pneumonia (including VAP),

ALI/ARDS, sepsis, renal failure, bleeding disorder and liver failure. Significant Spearman correlation coefficients were tested between the continuous predictor variables, before they were implemented in the regression models. Variables with less than three cases in one of the GOSE categories were not analysed. All variables reaching $P \leq 0.10$ in the univariable analyses were included in a multiple logistic regression model. In this model, we adjusted for the covariates age, GCS score and pupil dilation.

The precision of the estimates was assessed with 95% confidence intervals (CI). All tests were considered statistically significant at a probability value < 0.05. The statistical software Statistical Package for the Social Sciences version 18 (SPSS Inc., Chicago, IL, USA) or STATA/SE version 11.2 (StataCorp LP, College Station, Texas, USA) was used in all analyses.

Ethics

The study was done according to the principles of the Helsinki Declaration. Written informed consent was obtained from the patient, or if incapacitated from their next of kin. The Regional Committee for Medical Research Ethics approved the study.

Results

Demographics

Of the 133 included patients 79.7% were male and the median age was 30 years (range 1–81 years; Table 4). Twelve of the patients were less than 15 years (1–13.7 years). The majority of the TBIs were caused by either a traffic accident or a fall injury. The median GCS score before sedation was 6. One fourth of the patients had uni- or bilateral pupil dilation on admission. The initial CT findings often showed a combination of intracerebral pathologies with traumatic subarachnoidal haemorrhage (tSAH), subdural haematoma (SDH) and multiple contusions as the most frequent findings. In all seven patients with negative findings on CT examinations, the MRI showed diffuse axonal injury or cerebral contusions. Median ISS was 26 and median SAPS II in patients > 18 years was 43. One hundred and thirty of the 133 patients received invasive mechanical ventilation (0.5–34 days, median 6.0 days). 43.6% of the patients were operated for intracranial pathology and 43.6% were operated due to extracranial injuries.

Table 4

Patient demographics of the 133 included patients.

	Number of patients *n* (%)	Median (range)
Sex		
Male	106 (79.7%)	
Female	27 (20.3%)	
Age (years)		30 (1–81)
Cause of accident		
Traffic	70 (52.6%)	
Fall	54 (40.6%)	
Other	7 (5.3%)	
GCS score	131	6 (3–8)
Pupil dilation on admission	34 (25.6%)	
Unilateral	23	
Bilateral	11	
Injury Severity Score (ISS)	133	26 (5–54)
SAPS2 (> 18 years)	112	43 (21–91)
Cerebral CT findings*		
tSAH	97 (72.9%)	
SDH	81 (60.9%)	
EDH	24 (18.0%)	
Multiple contusions	70 (52.6%)	
Single contusion	7 (5.3%)	
Normal	7 (5.3%)	
Surgery for intracranial injury	58 (43.6%)	
Surgery for extracranial injury	58 (43.6%)	

*Many patients had more than one intracerebral pathology on cerebral CT.
EDH, epidural haematoma; GCS, Glasgow Coma Scale; SDH, subdural haematoma; tSAH, traumatic subarachnoidal haemorrhage.

Table 5

Registrated elevations in intracranial pressure (ICP) and reductions in cerebral perfusion pressure (CPP) in patients with ICP monitoring ($n = 105$)*.

	Number of patients ($n = 105$)	Patient data missing**
ICP 21–25 mmHg	26 (24.8%)	3
ICP > 25 mmHg	47 (44.8%)	3
CPP 60–69 mmHg	21 (20.0%)	3
CPP 50–59 mmHg	55 (52.3%)	3
CPP < 50 mmHg	20 (19.0%)	3

*Elevations in ICP and reductions in CPP are registered if measured ≥ 3 times/day.
**Missing data as a result of insufficient/lacking chart for one or more days.

Intracranial hypertension and treatment according to the three-level TBI protocol

ICP was monitored in 105 patients (78.9%). Out of the 105 patients with ICP monitoring, 29 did not have any episodes with elevated ICP, while 26 patients had episodes of ICP between 21–25 mmHg and 47 patients had episodes of ICP > 25 mmHg (missing ICP and CPP information in three patients) (Table 5).

About 75% of the patients with ICP monitoring received level 2 treatment due to high ICP and around 30% of the patients with ICP monitoring received level 3 treatment (all patients with level 3

treatment had also had level 2 treatment). Six of the patients with ICP monitoring did not have any episodes of CPP below 70 mmHg, while 21 patients had the lowest registration of CPP 60–69 mmHg and 55 patients had CPP 50–59 mmHg. A cerebral perfusion pressure below 50 mmHg was measured in 20 patients; three of them were children < 15 years old.

Deviations from other treatment goals

Almost two thirds of the TBI patients (65.4%) had periods of $PaO_2 \leq 11$ kPa during the ICU/HDU stay (Table 2). Hypotension was observed in 27 (20.3%) patients, 12 of them were children. Fifteen patients had low blood pressure during the first 24 h in the ICU/HDU. Anaemia (haemoglobin ≤ 100 g/l) was observed in 77.4% of the patients. A moderate hyperglycaemia (8–10 mmol/l) was frequent (39.1%), but a blood glucose above 10 mmol/l was rare (9.0%). One third (34.6%) of the patients had an observed serum sodium (S-Na) level of ≤ 135 mmol/l while 30.8% of the patients had hypoalbuminemia. Elevated body temperature was found in more than half of the patients (55%).

Extracranial complications during ICU/HDU stay

Pulmonary complications were a frequent finding with 73.7% of the patients having at least one of the following: VAP, pneumonia due to other causes, ALI or ARDS (Table 3). Pneumonia was the most common complication in TBI patients during the ICU/HDU stay. About one third (35.3%) of the patients had a VAP, whereas 37.6% had pneumonia due to other causes (one patient had both VAP and pneumonia due to aspiration).

ALI was diagnosed in 14.3% of the patients, whereas 17.3% met the definitions of ARDS. Most of the patients (83%) including all patients with ARDS, got vasoconstrictors during their ICU/HDU stay. Four patients (3%) had severe sepsis. One patient got a renal failure and needed continuous renal replacement therapy. Low platelets were found in six patients (4.5%). One of the patients had both low platelets and elevated bilirubin serum concentration and was classified as having a liver failure.

Prediction of outcome

Twenty-six (19.5%) of the 133 patients included died due to the head injury within the first 12 months; all but two died within the first month. Intracranial hypertension was the cause of death in 21 patients while five patients died due to sequels from their head injury. A good recovery (GOSE scores 7–8) was seen in 43 patients (32.3%), a moderate disability (GOSE scores 5–6) was seen in 34 patients (25.6%) and a worse outcome (GOSE score ≤ 4) in 53 patients (39.8%). One patient died of other causes 3 weeks after the TBI.

In the univariable analyses age, uni- or bilateral pupil dilation on admission and low GCS score were all highly associated with a worse outcome category (Table 6). Additionally, among the ICU/HDU observations, ICP > 25 mmHg, $PaO_2 \leq 11$ kPa, hyperglycaemia, pneumonia and ARDS were all significantly associated with a worse outcome. Hypotension (even if we excluded children ≤ 15 years), anaemia, hyponatremia, hypoalbuminemia, ALI and elevated body temperature were not associated to outcome.

In the multiple logistic regression with age, GCS score and pupil dilation as covariates, high ISS, ICP > 25 mmHg, S-Glu ≥ 8 mmol/l, and pneumonia were significantly related to a worse outcome. Intracranial hypertension with ICP less than 25 mmHg was associated with better outcome.

Discussion

After the implementation of a three-level protocol for treatment of patients with severe TBI, we found that deviations from the specific treatment goals were frequent. Almost three out of four patients got a pulmonary complication during the ICU/HDU stay, whereas other extracranial complications were infrequent. High ISS, hyperglycaemia, pneumonia and ICP > 25 mmHg predicted a worse outcome even after adjustment for the strong prognostic factors age, GCS score and pupil dilation.

Intracranial hypertension and degree of multi-trauma

The value of intracranial hypertension as a prognostic outcome factor is well established in earlier studies.[15,16] In our study, more than one third of the patients had ICP measurements above 25 mmHg, which was significantly associated with a worse outcome. However, for the patients with episodes of slightly increased ICP levels, we found no increased risk of a worse outcome.

While a study by Stocchetti et al. found that the frequency of surgical decompression and the use of barbiturates were restricted to less than 10% of patients with severe TBI, we found a relatively high incidence of level 3 treatment.[17] This is mostly

Table 6

Association with outcome.*

Variable	Univariate† *P*	Odds ratio (OR)	Confidence interval (CI)	Multiple logistic regression‡ *P*	Multiple logistic regression OR	Multiple logistic regression CI
Age	$P < 0.001$	1.04	1.02–1.06			
Pupil dilation	$P = 0.002$	3.57	1.62–7.88			
GCS	$P < 0.001$	0.71	0.59–0.86			
ISS	$P = 0.08$	1.03	0.996–1.06	$P = 0.006$	1.05	1.02–1.09
ICP						
21–25 mmHg	$P = 0.062$	0.45	0.20–1.04	$P = 0.021$	0.33	0.13–0.84
> 25 mmHg	$P < 0.001$	7.20	3.14–16.49	$P < 0.001$	7.40	2.93–18.71
$PaCO_2 \geq 5$ kPa	$P = 0.37$					
$PaO_2 \leq 11$ kPa	$P = 0.002$	3.23	1.54–6.81	$P = 0.12$		
Hypotension	$P = 0.84$					
S-Na ≤ 135 mmol/l	$P = 0.33$					
Hgb ≤ 100 g/l	$P = 0.13$					
S-Glu ≥ 8 mmol/l	$P < 0.001$	4.04	2.03–8.06	$P = 0.002$	3.33	1.53–7.26
Temp ≥ 38°C	$P = 0.101$	1.72	0.90–3.30			
S-Alb < 25 g/l	$P = 0.915$	0.999	0.98–1.02	$P = 0.71$		
Pneumonia	$P = 0.004$	2.99	1.43–6.28	$P = 0.048$	2.27	1.01–5.14
ALI	$P = 0.34$					
ARDS	$P = 0.030$	2.59	1.096–6.12	$P = 0.14$		

*The outcome ordinal variable = GOSE score 1–4 = poor outcome. OR greater than one indicates increased risk for worse outcome category, while OR less than one indicates decreased risk of worse outcome.
†Odds ration (OR) and confidence interval (CI) are only registered for variables with a significance value $P < 0.10$.
‡In the multiple logistic regression, age, GCS score and pupil dilation are covariates.
GCS, Glasgow Coma Scale; ICP, intracranial pressure; ISS, Injury Severity Score.

caused by the use of barbiturate infusion and hypothermia. The effect of decompressive craniectomy in treating cerebral oedema is controversial and only 6% of the patients in our study had a hemi/craniectomy.[18,19] In this study, nine patients received a lumbal drainage catheter, but four of the nine patients received lumbal drainage because of CSF leakage. However, occasionally, lumbal drainage is used and reduces ICP.[20] The treatment, still, is controversial due to the risk of cerebral herniation and this treatment is not a routine intervention in TBI patients.

The severity of the multi-trauma, measured by the ISS, predicted outcome independently after adjusting for other well-known prognostic factors. Previous studies of TBI patients have also shown that ISS could predict outcome.[21,22]

Deviations and outcome

Despite a desired blood sugar of 4.5–6.5 mmol/l during the study period, almost half of the patients (43%) in our study had episodes of hyperglycaemia > 8 mmol/l. The association with hyperglycaemia to a poor outcome observed in our study is in accordance with earlier studies.[23,24] However, the optimal blood glucose level in TBI patients is not established and several researchers advice against too strict blood glucose control due to the concern of hypoglycaemia, especially in the central nervous system.[25–28] Also, it is uncertain whether it is the blood glucose itself that is harmful to the brain or if the blood glucose level reflect the severity of the TBI.[29]

Our study could not find any significant relationship between hypotension in the ICU/HDU and a poor outcome. Several other studies have shown that early hypotension in patients with severe head injury is related to a poor outcome.[2,30] One explanation for this discrepancy can be that we addressed hypotension in the ICU/HDU and therefore did not include hypotension and hypoxia at the scene of accident or during the transportation to the hospital. Also, during established ICU treatment, some causes of hypotension such as hypovolemia are usually corrected, and therefore, a low arterial blood pressure is often not associated with decreased cardiac output and lower oxygen delivery. As oxygen delivery to the brain is a result of several factors, it may be that a combination of risk factors is more important than the presence of each isolated risk factor. The IMPACT study observed that the combination of early hypoxia and early hypotension was related to poorer outcome than if the patients had only one of the events.[30]

While the use of hypothermia in TBI patients is controversial, there is a general agreement to avoid hyperthermia.[8,31–33] A recent study from the Chinese head trauma bank indicates that both degree and duration of early post-injury hyperthermia are closely related to an unfavourable outcome.[34] However, we did not observe any significant relation between hyperthermia and a worse outcome.

We could not find any significant relationship between anaemia and a poor outcome. A review by Kramer and Zygun on anaemia and red cell transfusion in neurocritical care concluded that there are no randomised controlled trials related to the transfusion threshold among brain-injured patients.[35] Thus, the optimal haemoglobin level in TBI patients is not known. One third of the TBI patients had low albumin levels but in contrast to our earlier study, we did not observe that hypoalbuminemia was related to a worse outcome.[2] The importance of the albumin level in patients with TBI is uncertain. A post-hoc follow-up study from the SAFE (Saline or Albumin for Fluid Resuscitation in Patients with Traumatic Brain Injury) study concluded that fluid resuscitation with albumin to TBI patients was associated with higher mortality than resuscitation with saline.[36] Contrary to this finding is that the Lund concept use albumin as the main plasma volume expander and other studies that observe a negative relationship between low albumin and survival in the neurosurgical ICU patients.[37,38]

Extracranial complications and outcome

Pneumonia (including VAP) had a negative effect on outcome in our study. This agrees with a study by Piek et al. where pneumonia was one of the predictors of increased morbidity and mortality in TBI patients.[39]

Despite a high frequency of ARDS, only four patients had episodes of severe deviations in PaO_2 during their ICU/HDU stay. This low incidence of oxygenation failure suggests that the respiratory complication is usually possible to compensate with ICU respiratory interventions. There was no association between ALI, ARDS, hypo oxygenation and a worse outcome category. Previous studies in TBI patients are divergent; some studies have shown that ALI and ARDS are associated with higher mortality in TBI patients, while other studies fail to replicate this association.[40–43] The conventional TBI treatment includes the use of vasoconstrictors to keep an optimal cerebral perfusion pressure. We did not assess if the use of vasoconstrictor was due to increase CPP, circulatory instability or to counteract hypotension caused by sedation. It has been shown that the use of vasoconstrictors is associated with a higher incidence of ARDS.[41] The fact that all patients with ARDS in our study were given vasoconstrictors could support this association, but this is highly uncertain since most of the patients in our study received vasoactive medications.

The importance of treatment protocol for TBI patients in the ICU/HDU

Before the introduction of a treatment protocol for TBI patients, we performed a retrospective study on TBI patients in the ICU/HDU, including 133 patients with severe TBI during a 5-year period (1998–2002).[2] This study showed that hypotension, elevated blood sugar and hypoalbuminemia were possible predictors of an unfavourable outcome. The introduction of a treatment protocol for TBI patients resulted in a decrease in severe deviations of physiological parameters. For instance, a blood sugar level above 10 mmol/l was found in 26% in the retrospective study, while only 9% had severe hyperglycaemia in the prospective study. However, the frequency of patients with low albumin and hypotension were similar in both studies. The differences between frequency of deviation in physiological variables before and after an introduction of a treatment protocol suggest that the TBI treatment interventions that can be controlled and improved by the personnel (e.g. regulate the blood glucose with insulin infusion) are improved, while other factors may be more difficult to control due to the brain injury itself (e.g. brain oedema) and is less prone to be improved. As mentioned by Lingsma et al., it may also be that deviations in physiological variables are related to the severity of the brain injury, and that normalising the parameters does not necessarily improve the outcome.[29] This opinion is supported by Patel et al. who showed that patients with TBI observed between 1996 and 2003 showed less improvement in the adjusted odds of death since 1989 compared to patients without head injury.[5]

Limitations in the study

We have not analysed interactions between the different variables except for keeping the highly significant variables age, GCS and pupil dilation as covariates. We also have not analysed factors related to the treatment at the scene of accident and during the transportation to the hospital. Due to the observational nature of the study, the observed associations are not evidence for certain cause and effect

relationships. Finally, we have not taken into account the duration of the deviations in the analyses of outcome predictors.

Conclusion

Our study showed that deviations from specific treatment goals according to the treatment protocol of TBI patients were frequent also after the introduction of a TBI protocol. Pulmonary complications were common during the ICU/HDU stay, whereas other extracranial complications were infrequent. Age, GCS, pupil dilation, ISS, ICP > 25 mmHg, hyperglycaemia and pneumonia were all highly significant predictors of a worse outcome.

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Address:
Kari Schirmer-Mikalsen
Department of Anaesthesia and Acute Medicine
St. Olav University Hospital
Postboks 3250 Sluppen
7006 Trondheim, Norway
e-mail: kari.schirmer@stolav.no

Paper III

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Appendix 1-6

9. Appendices 1-6

Appendix 1. Glasgow Coma Scale score

Eyes	Open	Spontaneously	4
		To verbal command	3
		To pain	2
		No response	1
Motor response	To verbal command	Obeys	6
	To painful stimulus	Localizes pain	5
		Flexion- withdrawal	4
		Flexion- abnormal	3
		Extension	2
		No response	1
Verbal response		Oriented and converses	5
		Disoriented and converses	4
		Inappropriate words	3
		Incomprehensible sounds	2
		No response	1
Total			**3-15**

Appendix 2. SAPS 2 score

The worst value registered during the first 24 hours in the ICU. Only one total score per stay!
If dead or discharged before 24 hours, score values from time of admission to the ICU.

Admission	**Chronic disease**	**Age**	**GCS**	**Syst BP**	**HR**	**PaO_2/FiO_2**	**Score**
6 Medical	**9** Metastatic cancer	**7** 40 - 59	**5** 11 - 13	mmHg	/min	/	
8 Acute surgery	**10** Haematolgical cancer	**12** 60 - 69	**7** 9 - 10	**13** < 70	**11** < 40	**6** ≥ 26.6	
	17 AIDS	**15** 70 - 74	**13** 6 - 8	**5** 70 - 99	**2** 40 - 69	**9** 13.3 - 26.59	
3 Temp > 39		**16** 75 - 79	**26** < 6	**2** > 200	**4** 120 - 159	**11** < 13.3	
		18 80 -			**7** ≥ 160		
Diuresis ml/d	**Carbamide** mmol/l	**Leucocytes** 10^9/ml	**Potassium** mmol/l	**Sodium** mmol/l	**Bicarbonate** mmol/l	**Bilirubin** mmol/l	
4 500 - 1000	**6** 10 – 29.9	**3** > 20	**3** >5 eller <3	**1** ≥ 145	**3** 15 - 19	**4** 68.4 – 102.5	
11 < 500	**10** ≥ 30	**12** < 1.0		**5** < 125	**6** < 15	**9** ≥ 102.6	
						Total score	

Appendix 3. The SOFA score

The SOFA score is a daily score during the ICU stay. The worst value during every 24 hours should be registered.

	Score				
System	**0**	**1**	**2**	**3**	**4**
Respiration					
PaO_2/FiO_2, kPa (mmHg)	≥ 53.3 (400)	< 53.2 (400)	< 39.9 (300)	< 26.6 (200) + respiratory support	< 13.3 (100) + respiratory support
Coagulation					
Platelets, $10^3/\mu L$	≥ 150	< 150	< 100	< 50	< 20
Liver					
Bilirubin, µmol/L	< 20	20 – 32	33 – 101	102 – 204	> 204
Cardiovascular	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine < 5 or dobutamine (any dose)	Dopamine 5.1-1.5 or epinephrine/ norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine/ norepinephrine > 0.1
CNS					
GCS	15	13 – 14	10 – 12	6 – 9	< 6
Renal					
Creatinine, µmol/L	110	110 – 170	171 – 299	300 – 440	> 440
Diuresis				< 500 ml/d	< 200 ml/d
Total score					

SOFA, Sequential organ failure assessment; ICU, intensive care unit; PaO_2, partial pressure of arterial O_2; FiO_2, fraction of inspired O_2; MAP, mean arterial pressure; CNS, central nervous system; GCS, Glasgow coma scale score

Appendix 4. SAPS 3 score

(Based on http:/www.saps3.org)

The SAPS 3 is an ICU admission score (+- 1 h) and can predict vital status at hospital discharge. By admitting ICU, initial score is 16 p (Moreno et al., 2005).

		Group with lowest score		Highest value	Highest score
Age (years)		< 40	≥ 40 < 60, ≥ 60 < 70, ≥ 70 < 75 ≥ 75 < 80	≥ 80	18
LOS before ICU		< 14	≥ 14 < 28	≥ 28	7
Intra-hospital location before ICU		Operative room	Emergency room, Other ICU	Other	8
Co-morbidities					
	Cancer therapy	No		Yes	3
	Cancer	No		Yes	11
	Haematological cancer	No		Yes	6
	Chron. HF (NYHA IV)	No		Yes	6
	Cirrhosis	No		Yes	8
	AIDS	No		Yes	8
	Major therapy before ICU	No		Yes	3
ICU admission		Planned		Unplanned	3
Reasons for ICU admission	Cardiovascular	All others	Rhythm disturbance, hypovolemic/ septic shock	Anaphylactic, mixed / undefined shock	5
				Liver failure	
	Hepatic		Acute abdomen	Severe pancreatic	6
	Digestive		Coma, focal	Intracranial mass	9
	Neurologic	Seizures	neurological deficiency	effect	10
Surgical status at ICU admission		Scheduled surgery	No surgery	Emergency surgery	6
Anatomical site of surgery		Transplant	Trauma, cardiac surgery	Neurosurgery	5
Acute infection at	Nosocomial	No		Yes	4
ICU admission	Respiratory	No		Yes	5
GCS		≥ 13	5, 6, 7 - 12	3 - 4	15
Bilirubine	µmol/L	< 34.2	≥ 34.2 < 102.6	≥ 102.6	5
Temperature	°C	≥ 35		< 35	7
Creatinine	µmol/L	< 106.1	≥ 106.1 < 176.8, ≥ 176.8 < 309.4	≥ 309.4	8
Heart rate	/minute	< 120	≥ 120 < 160	≥ 160	7
Leukocytes	10^9/l	< 15		≥ 15	2
$[H^+]$, pH		> 7.25		≤ 7.25	3
Platelets	10^3/µl	≥ 100	≥ 20 < 50, ≥ 50 < 100	< 20	13
Systolic BP	mmHg	≥ 120	≥ 40 < 70, ≥ 70 < 120	< 40	11
Oxygenation	PaO_2/FiO_2 kPa	$PaO_2 \geq 8$	$PaO_2 < 8$ no MV, $PaO_2/FiO_2 \geq 13.3$ + MV	$PaO_2/FiO_2 < 13.3$ + MV	11
Total score		**Default 16**			

LOS, length of stay; ICU, intensive care unit; HF heart failure; GCS, Glasgow coma scale score; PaO_2, partial pressure of arterial O_2; FiO_2, fraction of inspired O_2; MV, mechanical ventilation.

Appendix 5. Injury severity score (ISS)

(From Trauma.org 20.04.2016, http://www.trauma.org/archive/scores/iss.html)

Region	Injury	AIS score		ISS example	ISS
Head and neck			0-5	1	
Face	Minor	1	0-5	2	Square of the 3 highest (0-5) scores and add e.g $5^2+3^2+2^2=38$
	Moderate	2			
	Serious	3			
Chest	Severe	4	0-5	0	
	Critical	5			
	(Unsurvivable	6)			
Abdomen			0-5	3	Max ISS= 75
Extremity			0-5	5	
External			0-5	0	

AIS, Abbreviated injury scale; ISS, Injury severity score. If AIS score is 6 in any of the regions, ISS will automatically be 75.

Appendix 6. Outcome scores

(Based on Nichol et al., 2011)

GOS (5 points)		**GOSE (8 points)**	
1. Dead		1. Dead	
2. Persistent vegetative	cannot interact, unresponsive	2. Persistent vegetative	
3. Severely disabled	Can follow command, cannot live independently	Severely disabled	3. Upper 4. Lower
4. Moderately Disabled	Can live independently, reduced work capacity	Moderately disabled	5. Upper 6. Lower
5. Good recovery	Can work	Good recovery	7. Upper 8. Lower

GOS, Glasgow outcome scale; GOSE, Glasgow outcome scale extended.
Study 1: GOS dichotomized into unfavorable (GOS 1-3) and favorable (GOS 4-5) outcome.
Study 2: GOSE was reclassified into worse (GOSE 1-4), moderate disability (GOSE 5-6) and good recovery (GOSE 7-8).