Current Concepts in Diagnosis and Treatment of Traumatic Brain Injury: Implications for Healthcare in Nepal

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Taumatic brain injury (TBI) is a leading cause of disability and death in the industrialized and in the developing world. With an incidence of 200-400 cases per 100.000, head injuries are a major contributor to socio-economic costs. The 20% suffering from severe head injury (SHI) requiring prolonged intensive care and/or neurosurgical intervention are of particular interest to specialist practitioners from multiple disciplines.

This review covers the current concepts of diagnosis and treatment in these patients in the Western world, i.e. mainly the US and Western Europe. Special emphasis is laid upon evidence-based guidelines established during the last decade. Comparison is drawn to the current status of trauma care in Nepal.

Management strategies for TBI can not be applied to Nepalese healthcare entirely. Effective management of head injured persons in Nepal is affected by its difficult geographical location, unavailability of trained personnel in the field, and difficulty in transporting the patients due to the lack of motorable roads. While some of the equipment for the treatment of TBI victims is readily available (e.g. ventricular drainage), others are scarce (e.g. operating room capacity, intensive care facilities) or completely unavailable (e.g. emergency medical service providers, specialized monitoring equipment). Realistic proposals for improvement of the current situation are made.

Key Words: cranio-cervical trauma, head injury, neurotrauma, traumatic brain injury

TBI is a leading cause of disability and death in both the industrialized and the developing world. With an incidence of 200-400 cases per 100.000, it is a major contributor to socio-economic costs. Especially those 20% suffering from SHI requiring prolonged intensive care and/or neurosurgical intervention are in the focus of neurotrauma specialists.

Severe head injury is defined as any disturbance in the structural integrity and functional homeostasis of the cerebrum by mechanical forces leading to prolonged coma. Its peak incidence is in the second to fourth decade of life with a male predominance. Road traffic injuries are the leading cause of TBI followed by falls and violence. In most large studies about 20–30% of patients with SHI are surgically treated for traumatic mass lesions and/or fractures. Treatment of SHI patients involves neurosurgeons as the lead specialists, even when approximately 2/3 of all patients are treated conservatively.

Following a brief introduction to the pathophysiology and classification of TBI we will review the current concepts in diagnosis and treatment of SHI according to published guidelines and our own observations. Regionally specific implications for the healthcare of Nepal will be added wherever applicable.

Pathophysiological Concepts

Manifestations of TBI can be differentiated as either primary or secondary injury. It has been known for several decades that the outcome of many SHI patients is signif- icantly affected by secondary insults to the brain, which

means that these insults occur at a time when they are already under supervision of healthcare professionals. Therefore the differentiation between primary and secondary injuries is clinically of the highest importance, as the dominating therapeutic concept in the treatment of SHI is the prevention of secondary injuries. This is demonstrated in **Figure 1**.

Primary injuries are, for example, hemorrhagic contusions, mechanical injury to nerve fibers (*diffuse axonal injury*) and vascular lesions directly caused by the traumatic incident.

Secondary injuries can be caused by intra- and extracranial disease processes. The latter are typically hypoxia and arterial hypotension since SHI frequently occurs in multiply-injured patients who might get into hemorrhagic shock.[67] Because the injured brain is especially susceptible to ischemia, avoidance of hypoxia and hypotension is of the highest importance. Pre-hospital as well as critical care management has to be carefully adjusted to these risk factors for secondary ischemic injuries.[11] Intracranial causes for deterioration are usually based on the primary injury, i.e. delayed intracranial hemorrhage into or worsening brain edema from a pre-existing lesion. The common pathway usually leads to increased intracranial pressure (ICP), lower cerebral perfusion pressure and finally malperfusion. Once compliance of the intracranial cavity reaches the lower threshold, the ICP may rise rapidly, leading to the known life-threatening sequelae of transtentorial and foraminal herniation of the midbrain and brainstem, respectively.

To date, we are still far from a treatment for SHI patients that takes these different neuropathological lesions into account. Developing targeted treatment-algorithms for SHI will be a goal for the future.

Classification of Head Injuries

Based on the integrity of the *dura mater*, head injury (HI) is classified as *closed* or *open*. *Indirect open* HI, e.g. small fractures of the frontal sinus or skull base fractures with tiny dural lacerations and transient liquorrhea and intracranial air, have to be differentiated from *direct open* HI with discontinuity of the skin overlying a skull fracture with dura laceration.

Clinical grading of HI into concussion, contusion and compression as well as grading according to the duration of unconsciousness has not been successful. Widely-accepted practice is to judge the severity of HI by the Glasgow Coma Scale (GCS).[84] Several points of critique have to be kept in mind however:

- Since the level of consciousness in head-injured patients is dynamic, the exact circumstances and the time of examination have to be taken into account;
- Judging the best examination is sometimes difficult for the inexperienced examiner (localizing vs. normal flexion vs. abnormal flexion);
- The scale has to be modified for pediatric patients, where the best verbal exam obviously depends on the developmental age.

Neurological examination in the pre-hospital environment is important, however it has its limitations given the process of rescue and transport. Single field measurements cannot be used for outcome prediction. It has been suggested to delay clinical grading of HI until hospital admission, resuscitate first and proceed with grading preferably prior to administering sedative or paralytic agents, or after these drugs have been metabolized. Then HI can be

Abbreviations used in this Review

AANS = American Association of Neurological Surgeons

ARDS = adult respiratory distress syndrome

BBB = blood brain barrier

CBF = cerebral blood flow

CBV = cerebral blood volume

CPP = cerebral perfusion pressure

CSF = cerebrospinal fluid

CT = computed tomography

CVR = cerebrovascular resistance

EBIC = European Brain Injury Consortium

EDH = epidural hematoma

EEG = electroencephalography

EMS = emergency medical service

EVD = external ventricular drainage

FDA = Food and Drug Administration

GCS = Glasgow Coma Scale

HI = head injury

ICH = intracerebral hematoma

ICP = intracranial pressure

ICU = intensive care unit

MAP = mean arterial pressure

SAH = subarachnoid hemorrhage

SDH = subdural hematoma

SHI = severe head injury

TCDB = Traumatic Coma Data Bank

TBI = traumatic brain injury

THAM = tris buffer

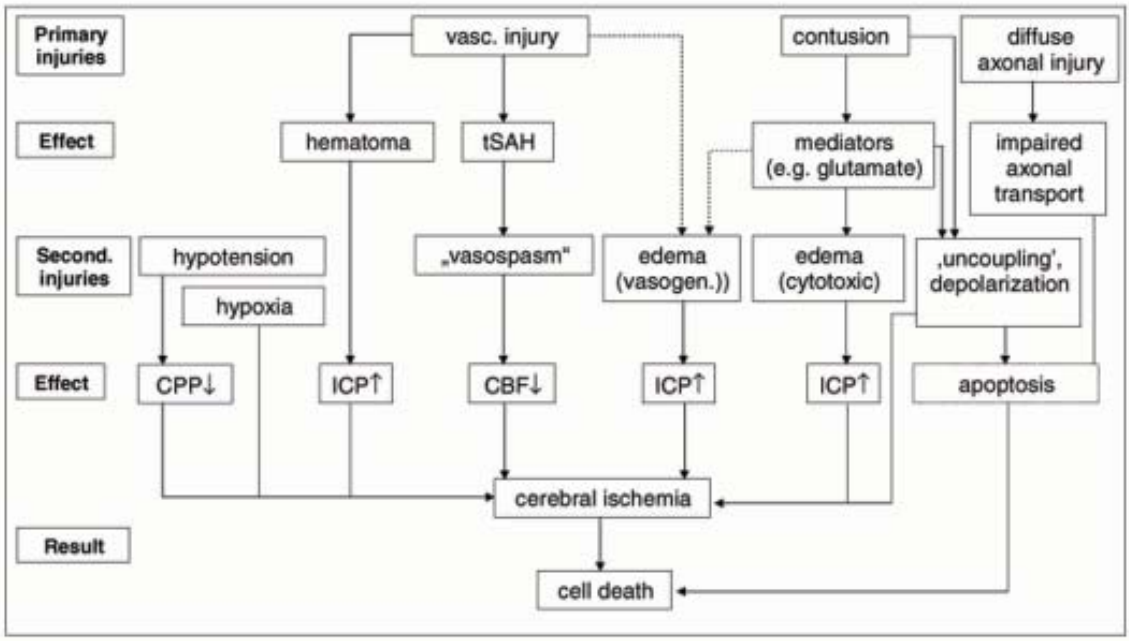

Figure 1.Pathophysiological concept of secondary injuries; cerebral blood flow (CBF), cerebral perfusion pressure (CPP), intracranial pressure (ICP), traumatic subarachnoid hemorrhage (tSAH).

classified according to the post-resuscitation GCS as follows:

- Mild HI: GCS 13 – 15;
- Moderate HI: GCS 9 – 12;
- Severe HI: GCS 3 – 8.

Another classification of HI, which is based on computer-tomographic criteria of intracranial lesions, has been suggested by Marshall and co-workers **(Table 1).** [62]

Pre-hospital Treatment

Emergency Medical Services (EMS) providers are often the first healthcare providers for patients with TBI. Treatment often begins in the field by EMS providers who have varied skills, backgrounds, and qualifications. They continue this care *en route* to the hospital. Thus, prehospital assessment and treatment is the first critical link in providing appropriate care for individuals with severe brain injury. Based on this conception the "Brain Trauma Foundation" (www.braintrauma.org) was the first group to develop evidence- based guidelines for the pre-hospital management of SHI patients.[27] General differences, however, arise from the organization and strategy of EMS providers (*scoop and run* vs. *stay and play*). A simple pathway, based on the situation in many European countries, i.e. emergency physician sent out directly with or called secondarily by paramedics (*rendezvous* system), is outlined in **Figure 2.**

Repeated measurements of the GCS should be obtained as soon as possible, with any score of less than nine or decline by two points indicating serious injury. Examining the pupils is also a standard component of the neurological examination and is particularly important in evaluating patients with TBI.

Trained medical personnel should measure oxygenation and blood pressure. Hypoxemia (<95% arterial hemoglobin oxygen saturation) or hypotension (<90 mm Hg systolic blood pressure) have to be avoided throughout rescue and transport. Isotonic crystalloid solutions are commonly used for fluid resuscitation, but "small-volume resuscitation" with fluids like hypertonic saline with or without dextran has been used with some success. The pre-hospital use of mannitol carries the risk of volume depletion and is generally not recommended. Patients with HI of any grade and other systemic injuries frequently deteriorate and become respiratory insufficient. The threshold to intubate should be low. All patients with SHI (GCS <9) should be intubated and normoventilated in the field. Prophylactic hyperventilation probably induces more risks than benefits through cerebral vasoconstriction. Therefore, it is not recommended and should be reserved for patients with signs of cerebral herniation, such as extensor posturing or pupillary abnormalities (asymmetric or unreactive) after correcting hypotension or hypoxemia.

Sedation, analgesia, and neuromuscular blockade can be useful to optimize transport of the head-injured patient. To avoid intoxication and, for example, profound hypotension these medications should be used sparingly. The need for repeated neurological assessments should also be kept in mind.

Regarding transport decisions it is recommended that patients with mild and moderate HI at least need evaluation at a trauma center. Patients with SHI, however, receive optimal care at a facility identified as having the following capabilities: immediately available computed tomography (CT) scanning, prompt neurosurgical care, and the ability to monitor intracranial pressure and treat intracranial hypertension.

Diffuse trauma I	No changes visible on CT
Diffuse trauma II	Open cisterns, no midline shift, hyperdense or mixed-density lesions < 25 ml, no bone fragments or foreign bodies
Diffuse trauma III	Compressed or invisible cisterns, midline shift 0-5 (brain swelling) mm, hyperdense or mixed-density lesions <25 ml
Diffuse trauma IV	Hyperdense or mixed density lesion < 25 ml, (shift) midline shift > 5mm
Removed lesion	Any surgically removed lesion
Non-removed lesion	Hyperdense or mixed-density lesions >25 ml

Table 1. Computer tomographic classification of traumatic brain injury (according to Marshall et al.[62])

Hospital Treatment

Diagnosis

Adequate use of diagnostics has to be made in the work-up of HI. Since the clinical grade is the best predictor for serious TBI it is also used for diagnostic decision-making.

In patients with mild HI, CT is not necessarily indicated, as long as the neurological exam is normal, there is no hemorrhagic diathesis (e.g. anticoagulant use) or mechanism of accident that is not suggestive of high kinetic forces affecting the cranium. Conventional radiography is too insensitive as a screening method.[54] In case of a skull fracture a CT should be obtained to rule out intracranial hematoma. Clinical observation of patients with mild HI is always indicated, if observation by relatives or friends is not feasible.

Patients with moderate HI should have a CT. Hospital admission for close neurological monitoring is recommended, since deterioration to a higher clinical grade is frequent.

Patients with SHI are, by definition, comatose. As soon as possible following hospital admission, CT scanning should be undertaken to rule out mass lesions requiring surgical evacuation. Also, the indication for intracranial pressure monitoring is positively confirmed with any abnormal CT in this patient group.

Operative Treatment

Introduction

Initial operative, neurosurgical treatment for closed HI involves two types of injury:

1. Traumatic intracranial hemorrhages;
2. Impression fractures

Traumatic intracranial hemorrhages are a direct consequence of the primary injury, i.e. disruption of the vasculature supplying meninges and cerebrum. Evacuation of space-occupying hemorrhages is a first step to minimize secondary injuries to the brain.

Extradural (or epidural) and intradural hemorrhages have to be differentiated. The latter are defined by localization as subdural, subarachnoidal or intracerebral. Intracerebral hemorrhages can extend into the ventricles and be either manifestations of intracerebral vessel rupture or a hemorrhagic contusion. All types of hemorrhage can commonly coexist, with hemorrhagic contusions being the most frequent lesions.

Epidural Hematoma

An epidural hematoma (EDH) is usually associated with a skull fracture. Frequent sources are arterial vessels of the dura, but leakage from fractured bone edges also occurs. EDH are especially frequent in the temporal region (75%), less frequent in the frontal (11%), parietal (3%), occipital (6%) regioms or in the posterior fossa (7%).[44] Adhesions of the dura along the sutures of the skull are limiting to the extension of EDH and cause a typical appearance of biconvex (or lentiform) morphology on CT (**Figure 3**). Clinical symptoms of EDH are nonspecific: usually there is a decreased level of consciousness, that is progressively worse over time. The "typical" course of a lucid interval that is followed by unconsciousness and anisocoria is observed in less than 10% of those with EDH.

Rapid operative evacuation and thorough hemostasis is the key treatment for EDH. Some authors suggest conservative treatment in conscious patients (GCS >8), without focal neurological deficit, if the hemorrhage is small (<30 ml) and without significant shift (<5 mm). Then, however, the necessity for repeated CT scans (˜ 6-12 hours apart) has to be stressed.

The prognosis for patients with EDH is dependent on their clinical exam and severity of associated injuries. Overall the outcome of patients without additional intracranial lesions and with adequate surgical treatment is favorable.

Acute Subdural Hematoma

According to Cooper, subdural hematomas (SDH) are subdivided into the acute SDH, subacute SDH and chronic

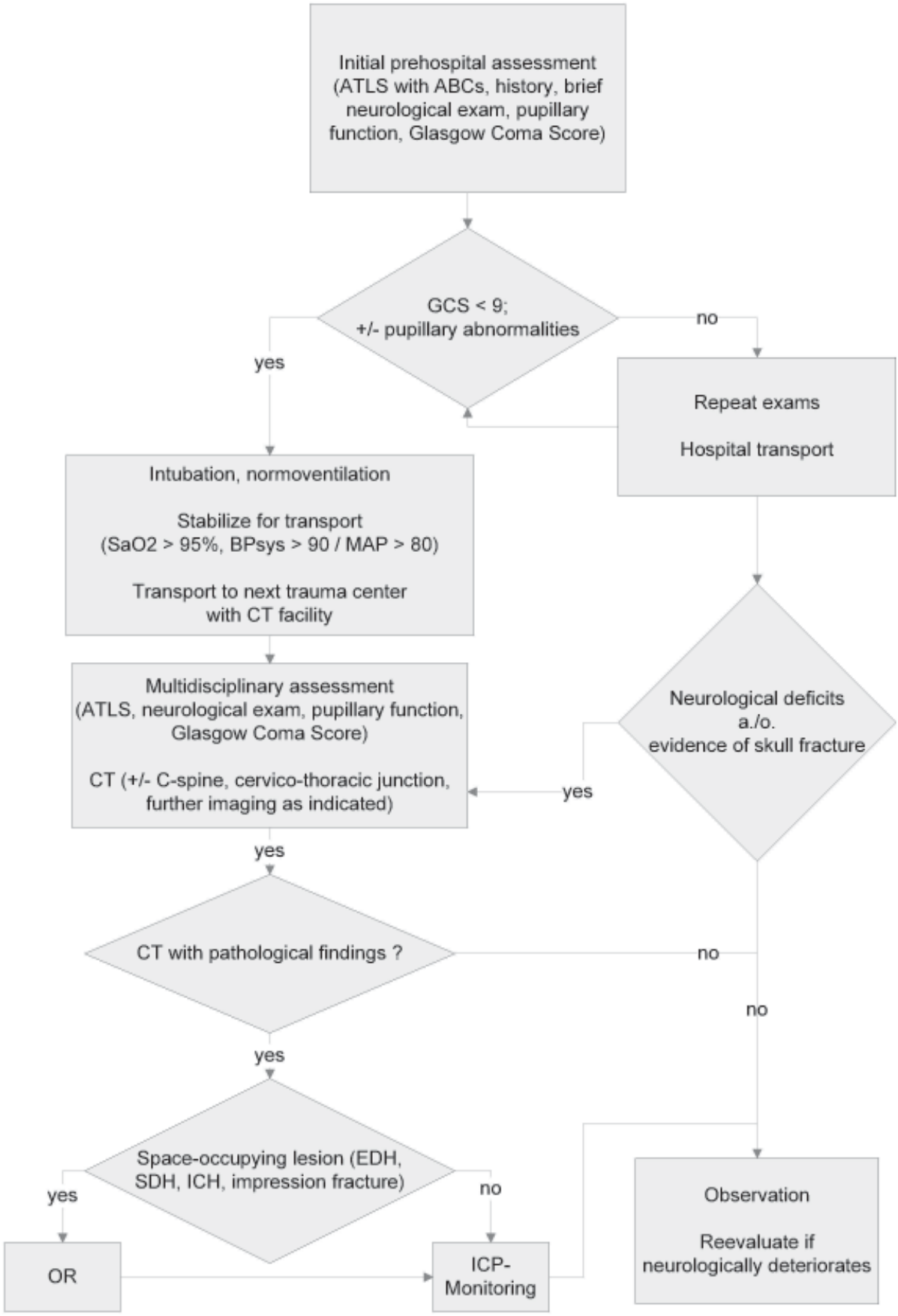

Figure 2. Algorithm for the prehospital management of head-injured patients; Advanced Trauma Life Support (ATLS), epidural hematoma (EDH), Glasgow Coma Scale (GCS), intracerebral hematoma (ICH), intracranial pressure (ICP), mean arterial pressure (MAP), Operating room (OR), subdural hematoma (SDH).

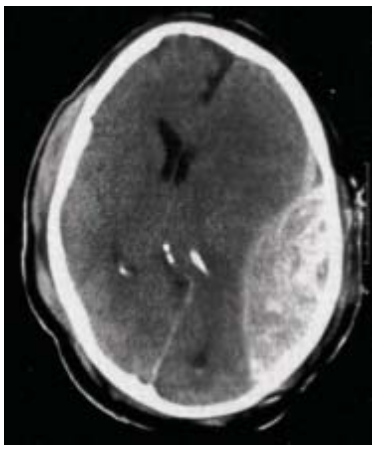

Figure 3. Computed tomography of head of a patient with a left-temporal epidural hematoma. Note the profound midline shift.

SDH.[15] Acute SDH are usually symptomatic within 72 hours after trauma. They are hyperintense and concave- shaped on CT. Intraoperatively they present as a coagulated subdural clot. Subacute SDH usually have a delayed onset of symptoms, ranging from 3–20 days. They are less hyperintense or isodense depending on how much of the hematoma is liquified. The chronic SDH usually take longer than 20 days until clinical onset. On CT they appear hypodense, rarely isodense. Upon drainage they typically present as brownish fluid with or without membranous compartments.

Sources of SDH are ruptured bridging veins or hemorrhagic cortical contusions. Hemorrhagic contusions are frequent in fronto-temporal regions. SDH spreading over the whole hemisphere represent a significant intracra nial mass lesion with subsequent increase in ICP and midline shift (**Figure 4**). Pre-existing hematological diatheses, for example, secondary to severe alcohol abuse, are predisposing factors for SDH.[40]

The clinical symptomatology is nonspecific. Most important is the decreased level of consciousness, or even unconsciousness with or without signs of tentorial herniation caused by the mass effect of SDH.

Acute SDH are surgically evacuated unless they are thin (<10 mm and <5 mm midline shift, i.e. *pancake hematomas*) and not affecting the level of consciousness. In comatose patients with a GCS <9, ICP monitoring is recommended in either case. Surgical techniques are manifold, careful hemostasis being the key to success in most of them. In patients with post-traumatic swelling and therapy-refractory intracranial hypertension, the craniotomy site can be easily enlarged for decompression and a duraplasty be performed. As a *second-tier*-therapy the value of decompressive hemicraniectomy is currently more and more appreciated. Prophylactic decompression, invaluable in individual cases, still remains under debate.

Much as in EDH, the prognosis of acute SDH is dependent on the initial clinical presentation and severity of associated injuries. Overall, however, cerebral lesions are more common with SDH and therefore mortality remains high.[94] In the American Traumatic Coma Data Bank (TCDB) study, mortality in young patients with acute SDH was about 40%.[60]

Traumatic Intracerebral Hematoma

Traumatic intracerebral hematomas (ICHs) are inhomogenous in size and localization. In SHI they are the most frequent neuropathological lesions. The CT classification by Marshall et al., includes these lesions in groups II–IV.[62] Again the fronto-temporal poles of the cerebrum are the most frequent localizations (**Figure 5**). Biomechanics of rapid acceleration and deceleration with HI explains so called *contre-coup* lesions, leading to association of frontal and occipital contusions as well as bitemporal contusions. Disorders of hemostasis or coagulation, especially with severe alcoholism, are predisposing factors. These hemorrhages are usually small and diffusely spread and therefore rarely surgically removable. Conservative treatment is commonly preferred, unless ICP becomes therapy-refractory. In such cases operative decompression may be indicated secondarily. In the case of isolated, single lesions measuring more than 25 ml on CT surgical removal has been suggested.[62] Others suggest evacuation of lesions measuring 20 ml and above if mass effect by radiographical criteria is present, and definitely in any lesion measuring 50 ml and more.[63]

Impression Fracture

Impression fractures can be an indication for surgical intervention in HI. Certainly every significantly space-occupying impression fracture should be elevated (**Figure 6**). Traditionally closed impression fractures are operated whenever the impression of the outer table of the skull exceeds the inner table limits. This view, however, underlies considerable variation among surgeons. Great caution is advised with any impression fracture involving the dural venous sinuses.[47,57]

Posttraumatic Hydrocephalus

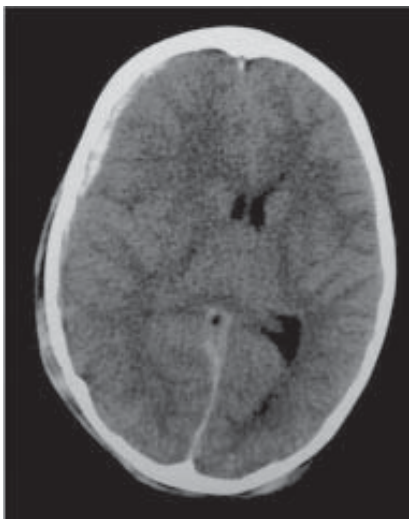

Figure 4.Computed tomography of head of a pediatric patient with a right-sided, acute subdural hematoma. Note the profound midline shift.

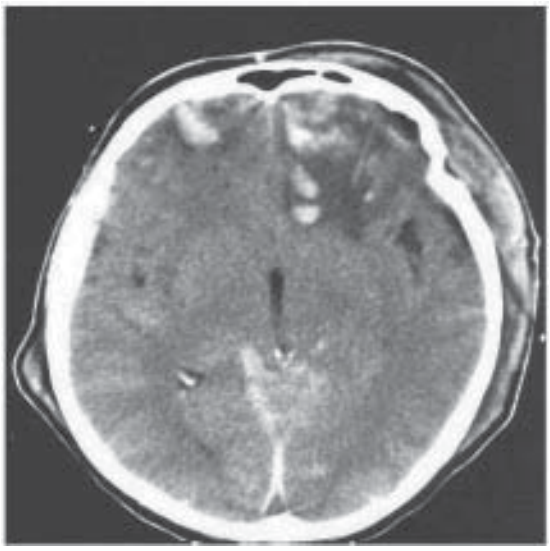

Figure 5. Computed tomography of head of a patient with bifrontal contusions.

Posttraumatic hydrocephalus is one of the chronic sequelae of SHI (**Figure 7**). The American TCDB study revealed a total incidence of 5.5%. These patients also had a significantly worse outcome compared to patients without hydrocephalus.[60] Consequently the posttraumatic hydrocephalus should be adequately treated, i.e. through implantation of a shunt-system. Of all hydrocephali, 88% manifest within 6 weeks after trauma. Therefore repeat CT scanning is recommended in that time frame. In patients who do not improve or whose improvement arrests prematurely, another CT scan within 3 months following trauma should be obtained.[10] Which patients benefit most from shunting depends on a number of factors and is beyond the scope of this review.

Monitoring

In monitoring SHI patients basic practices have to differentiated from extended neuromonitoring. **Table 2** gives an overview of parameters that are commonly monitored in SHI patients. A combination derived from basic and extended neuromonitoring is the so called multimodal (or multiparametric) cerebral monitoring.

Basic Monitoring

Basic monitoring of common physiological parameters is mandatory for all patients with SHI, especially those with increased ICP.[57] Basic monitoring is not different from the monitoring applied in other critical care patients. Discontinuous blood pressure monitoring (using the Riva-Rocci method) may be sufficient in mild or moderate HI, whereas SHI patients require continuous, automatic blood pressure measurements to ensure stability in the mean arterial pressure (MAP) (and thus cerebral perfusion pressure (CPP)). For this pressure transducers need to be leveled with the ICP measurement. Conventionally the external acoustic meatus is chosen as a reference. Arterial lines, nowadays standard in many intensive care units (ICUs), have a low procedural and low infectious risk and are furthermore helpful for routine blood gas analyses. Additionally continuous monitoring of the arterial oxygen saturation curve is fairly simple and cheap. Both blood gas analyses and saturation monitoring complement each other and have become *conditio sine qua non* in modern intensive care medicine. According to the recommendations of the European Brain Injury Consortiums (EBIC) the following arterial blood gas parameters should be maintained: arterial saturation of oxygen >95%, arterial partial pressure of oxygen (p_aO_2) >100 mmHg, arterial partial pressure of carbondioxide (pCO_2) >35 mmHg.[57]

With the renaissance of hypothermia monitoring of core temperature has been intensified in neurosurgical ICUs. It is well known that hyperthermia aggravates TBI by increasing energy metabolism and demand.[32] Therefore hyperthermia ought to be treated aggressively in all patients with cerebral lesions. Hemoglobin concentrations should be maintained above 10 g/dl in all SHI patients. Since both hypo- and hypernatremia increase the risk for edematous brain swelling, prevention or cautious normalization needs to be undertaken. Several studies have shown that hyperglycemia is associated with significantly worse clinical outcomes.[45,95] Consequently, normoglycemia is the goal in all SHI patients.

Bleeding and hypocoagulable states are frequently seen with TBI and may contribute to enlarging hemorrhagic contusions as well as traumatic intracerebral hematomas.[34] Monitoring and stabilization of coagulation parameters are paramount objectives in the care of SHI patients.

Clinical Neurological Monitoring

During the last decade intracranial pressure monitoring, calculation of cerebral perfusion pressures, evolving microsensor technology, etc. have changed the perception

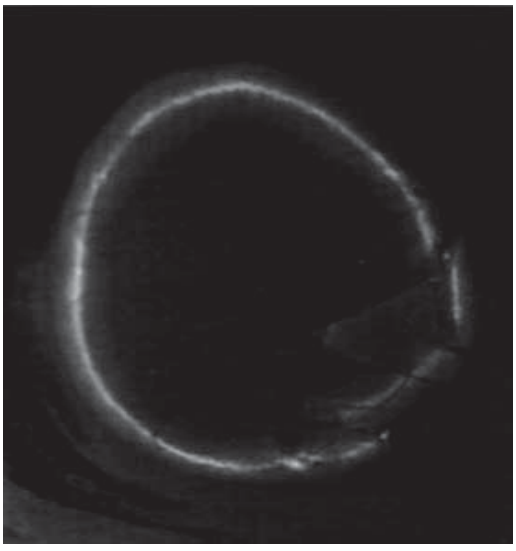

Figure 6. Computed tomography (bone window) of a patient with severe head injury with a left parietal impression fracture.

A. Basic Monitoring:		
	Common	Electrocardiogram (ECG)
		Respiratory rate
		Pulse oximetry
		End expiratory CO2 (ETCO2)
		Blood pressure (MAP)
		Temperature
		Blood gas analysis (pO2, pCO2, pH)
		Blood chemistry (Hb, Hkt, electrolytes, coagulation status, plasma osmolarity
	Cerebral	Neurological status (GCS)
		Intracranial pressure (ICP)
		Cerebral perfusion pressure (CPP)
B. Extended Monitoring:		
		Jugular bulb oximetry
		Brain tissue oximetry
		Microdialysis
		Thermal diffusion CBF
		Transcranial Doppler (TCD) sonography
		Electroencephalography (EEG), evoked potentials
		Electrocorticography

Table 2. Monitoring of severely head-injured patients.

of clinicians involved with HI patients. Previously, clinical neurological examination was the only means of monitoring. In patients with mild or moderate HI clinical assessment still is the most important information. By using the GCS the level of consciousness in trauma patients can be followed efficiently in a standardized fashion.[84] In SHI patients, however, clinical assessment and the value of GCS scoring is limited. Patients are usually intubated, sedated and therefore not able to open their eyes or verbally respond. Still, the best motor response can be an important indicator for neurological deterioration. Whenever possible sedation should be paused for neurological assessments in a scheduled fashion, the only exception to this being patients with critically increased ICP.

Any decrease in the GCS by two or more points is clinically significant and additional diagnostic efforts, e.g. CT scanning, should be taken to rule out developing intracranial pathology.

Additionally, careful examination of the pupillary light response, symmetric width of the pupils and caudal cranial nerve functioning is substantial and may be used to confirm ICP measurements or question artificial readings. Focal neurological deficits, like, hemiparesis mandate diagnostic work-up including CT.

Cerebral Monitoring (ICP / CPP)

Monitoring and treatment of ICP is meant to reduce the number and severity of secondary ischemic injuries to the brain. As such it is an indirect measurement. Intracranial hypertension can only be treated adequately with consequent measurement of the ICP.[36,55] In SHI, intracranial hemorrhages, contusions, pericontusional edema or global brain edema can be the cause for increased ICP and reduced CPP.[89] ICP should be monitored whenever these lesions are present, especially in conjunction with compressed basal cisterns.[7] In unconscious patients with SHI and a normal CT the risk for intracranial hypertension is increased if at least two of the following items apply:

- Age 40 and above;
- Flexor or extensor posturing;
- Systolic blood pressure less than 90 mmHg.

ICP monitoring is not indicated in patients with mild or moderate HI where the neurological exam can be followed (i.e. GCS >9). In the presence of massive cerebral contusions there is always a risk for sudden deterioration, so that in patients who are "on the edge" the indication for placement of an ICP monitor needs to be assessed individually.

The hydrostatic pressure derived from the frontal horn of the lateral ventricle via an external ventricular drainage (EVD) is the "goldstandard" for ICP measurement. By definition ICP is referenced to the level of the *Foramen of Monro*. This is in line with the external acoustic meatus, which serves as a skin landmark when leveling pressure transducers. An argument in favor of a ventriculostomy is the therapeutic value of cerebrospinal fluid (CSF) drainage, while the risks of infection and hemorrhage have to be contemplated.[71]

Direct measurement by tip transducers placed in the brain parenchyma has a significantly lower morbidity, but the system cannot be recalibrated after implantation and is prone to drift and technical error.[28] Epidural measurements of the ICP depend on dural tension and are technically

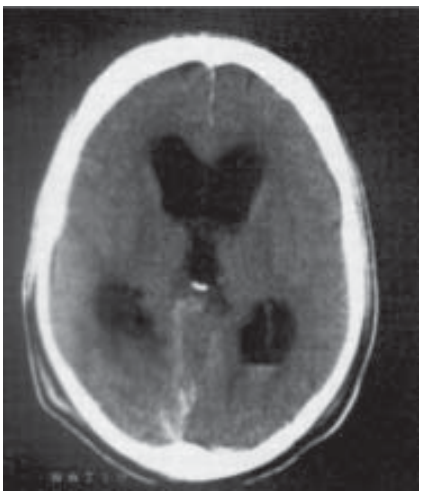

Figure 7. Computed tomography of head of a patient with post-traumatic hydrocephalus.

inferior to the aforementioned systems. Especially overestimations of ICP have been found, so that epidural ICP monitors are used less nowadays.[8] According to theoretical considerations the intracranial compliance (i.e. the volume that leads to a certain increase in ICP) should be a more sensitive parameter for impending deterioration. In clinical practice, attempts to measure intracranial compliance continuously have encountered too many technical problems.[49] The routine use of ICP measurements, when indicated, takes precedence over the specific technical system chosen. Technical errors and uncertainties are diminished with frequent application, so that the number of different ICP monitors at a given institution should be kept low.

Even though ICP is measured continuously, in clinical practice the mean value of ICP is regarded. Usually recordings are taken end-hourly.[59] The threshold for intervention is 20 mmHg since the neurological outcome of SHI patients seems to be affected the more the longer the ICP stays above this level.[66] It has to be underscored, however, that an ICP of 15–20 mmHg is already pathologically elevated.

Up to date there is no prospective randomized clinical trial to prove the impact of ICP monitoring and treatment on functional outcomes of SHI patients. For obvious ethical reasons such a trial will never be run. Meanwhile there are many findings that show a beneficial impact of ICP monitoring indirectly. In the US American guidelines this is discussed in great detail.[7,22,30] For instance, CSF-drainage has been shown to improve the outcome following SHI.[29] The odds for dying from SHI clearly correlate with the cumulative time the ICP is >20 mmHg.[58]

Cerebral perfusion pressure (CPP = MAP - ICP) is, by definition, linked to ICP. It has been known for long, that with CPP decreasing below the threshold for autoregulation, cerebral perfusion is diminished and finally ceases.

Figure 8 illustrates the relationship between ICP, CPP, cerebrovascular resistance (CVR) and cerebral blood volume (CBV). According to the CPP- management concept (*vide infra*) this pathway can be reversed and used therapeutically, if pressure autoregulation is intact:

1. Any increase in ICP reduces CPP consecutively. This results in vasodilation (i.e. reduced CVR to maintain cerebral blood flow (CBF)) and CBV increases subsequently Then a "vicious cycle" with steadily rising ICP is started;
2. Decreased ICP, on the other hand, augments CPP leading to vasoconstriction and reduced CBV. This mechanism allows sustained lowering of ICP.

It is conceived, if cerebral pressure autoregulation is intact, any augmentation of MAP results in decreased ICP. This assumption may be oversimplified, however. Experimentally it has been shown that besides increasing MAP, catecholamines do affect neuronal activity, vasoactive mediator release, cerebral metabolism and extracellular amino-acid transmitter concentrations.[52]

The crucial question is, where this pressure threshold exactly is in individual patients. Several techniques to estimate the autoregulation threshold, both invasive and non-invasive, have been suggested.[18,81] By using jugular venous bulb oximetry and transcranial Doppler sonography the breakpoint was determined to be 70 mmHg.[9] Others have shown a slightly lower threshold (60 mmHg) by brain tissue and jugular bulb oximetry.[50] Accordingly it is suggested to maintain the CPP above 60 mmHg, with a tendency to keep it in the upper range to have a buffer zone for adequate cerebral perfusion and oxygenation.[2,6,9,50,53,76]

Regarding the critical question whether ICP or CPP should be followed, many arguments have been raised based on clinical and experimental findings. Currently it has to be stated that both need to be regarded in the treatment of SHI. Two different concepts of SHI treatment are of general interest:

The so-called "Lund" (*volume-targeted*) therapy regimen is based on the concept that vasogenic edema has a major impact on intracranial hypertension following HI.[2] By moderate beta-blockade blood pressure is reduced and dihydroergotamine is used to reduce the cerebral blood volume by venoconstriction. Both measures should lead to a significant reduction in vasogenic edema and thus ICP. This results in a CPP >60 mmHg.[2] To date, one non-randomized, prospective study has shown a significant beneficial effect on outcome using volume targeted treatment.[23]

The contrary concept of CPP-management (*CBF-targeted*) assumes that with preserved cerebral pressure autoregulation any rise in MAP will lead to a decrease in ICP. The resulting CPP is affected positively. In clinical practice blood pressure is elevated by catecholamines. Individually MAPs of 100 mmHg or higher are necessary.[76] On the one hand cerebral blood flow and parameters of cerebral oxygenation are positively affected, on the other hand there are significant risks associated with this treatment (e.g. the development of adult respiratory distress syndrome (ARDS)).[14,74]

Both therapy regimens are not diametric to each other since they have in common that ICP is treated whenever >20 mmHg and CPP is maintained at >60 mmHg.

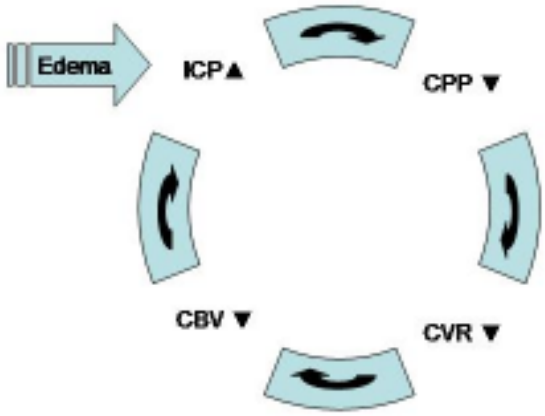

Figure 8. Vicious circle of increased intracranial pressure triggered by brain edema; cerebral blood volume (CBV), cerebral perfusion pressure (CPP), cerebrovascular resistance (CVR), intracranial pressure (ICP).

In conclusion, the European Brain Injury Consortium (EBIC) and the American Association of Neurological Surgeons (AANS) have suggested the following thresholds for intervention: ICP 20 mmHg, and CPP 60 mmHg (**Figure 9 and 10**).[6,7,57] To maintain a CPP of 60 mmHg the ICP should be kept lower than 20 mmHg by conservative treatment measures. If this fails the use of catecholamines should be considered. In a recent novel to the AANS guidelines (2003) prophylactic elevation of the CPP beyond these targets, however, has been discouraged.[6] A comparison of ICP-oriented therapy against CPP-oriented therapy has not shown any influence on the neurological outcome.[74] At least an elevation of CPP above 70 mmHg,, has therefore been called into question.[74,76,82]

Extended Cerebral Monitoring (Oxygenation, Metabolism, Cerebral Blood Flow)

As mentioned earlier, ICP/CPP monitoring yields surrogate parameters to avoid deterioration of cerebral perfusion in comatose patients. Normal or moderately increased ICPs, however, are only indirect indicators of sufficient perfusion, whereas a high ICP is not necessarily a herald of pending ischemia. In the early 90's high expectations had been raised by the emerging field of (direct) invasive cerebral oximetry. Here a sensor is placed in a representative region of the brain (e.g. tissue oximetry, $p_{ti}O_2$), in the jugular-venous return from the cranium (jugular bulb oximetry, $S_{jv}O_2$), or (non-invasively) on the skin and adjacent to the region of interest (near-infrared spectroscopy, NIRS). A clear distinction has to be made between global and local measurements. Both $S_{jv}O_2$ and $p_{ti}O_2$ are sensitive parameters for the risk of an unfavorable outcome, if desaturations (<50%) or critical decreases in the partial pressure of oxygen occur frequently (<10 mmHg). Both measurements allow for a more individualized (targeted) ICP/CPP therapy.[74,90]

In the last decade the so-called *bedside-* or *online-*microdialysis has been introduced in neurocritical care. This method is based on a double-lumen microcatheter with a semipermeable membrane in the cerebral parenchyma. Neurochemical analyses of the cerebral extracellular space can be performed using an automated photometer. Within minutes information about concentrations of glucose, lactate, pyruvate, glutamate and glycerol in the brain becomes available to the clinical team and can be used for therapeutic decisions.[41,86] Several studies have demonstrated the safety and feasibility of the method. One important aspect was to confirm the critical threshold for *pti O*2 (<10 mmHg, Licox^{TM} Sensor) on the basis of metabolic impairment. A safety margin of 5 mmHg (i.e. *pti O*2 15 mmHg) appears useful to avoid manifest hypoxia (**Figure 11**).[50,77] Overall it can be stated that the use of microdialysis in HI is still investigational, but, especially in combination with brain tissue oxygenation, a detailed picture of tissue energy metabolism and integrity can be made.

Following ICP, CPP, tissue oxygenation and neurochemical monitoring a continuous and quantitative method to measure cerebral blood flow directly has been demanded. Up to now, CBF monitoring was technically unsatisfying. A probe that is placed in the brain parenchyma and allows stable CBF readings based on the principles of thermodilution in perfused tissues has now been cleared by the Food and Drug Administration (FDA) recently (Q flow 500 probe, Bowman Perfusion Monitor, Hemedex, Cambridge, MA). A good correlation has been shown with stable Xenon-CT.[91] It is expected that this method will face critical clinical testing during the next few years.

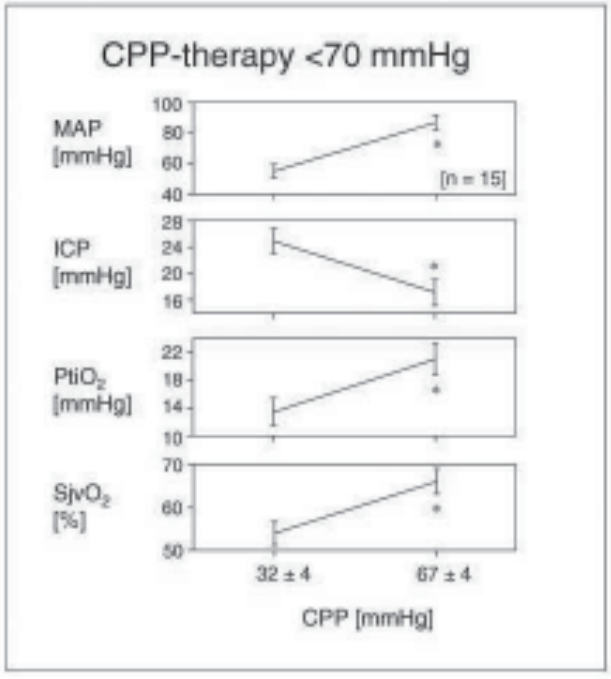

Figure 9. Effect of elevating blood pressure in patients with severe head injury and concomitant arterial hypotension. Infusion of dopamine increases mean arterial pressures from 55 mmHg to 90 mmHg leading to decreased intracranial pressure and improved cerebral oxygenation ($p_{ti}O_2$, $S_{jv}O_2$); cerebral perfusion pressure (CPP), intracranial pressure (ICP), mean arterial pressure (MAP), partial pressure of oxygen in brain tissue (ptiO2), jugular-venous saturation of oxygen (sjvO2).

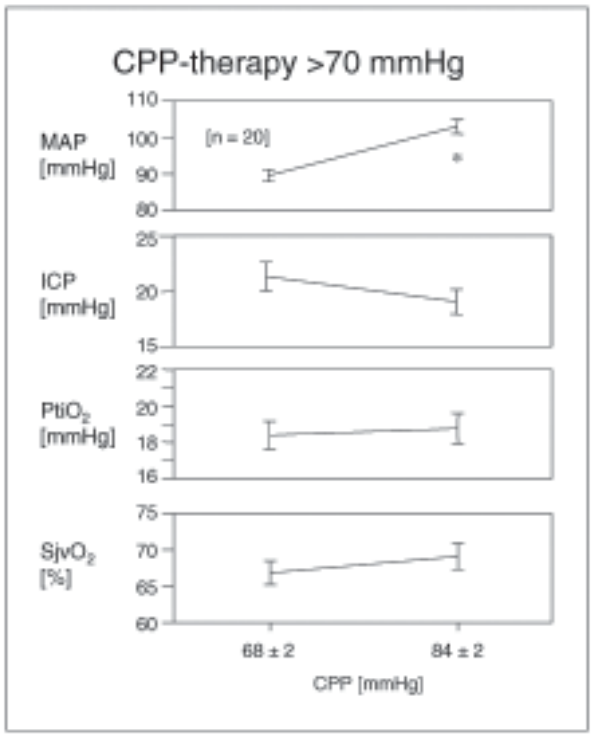

Figure 10. Effect of elevating blood pressure in patients with severe head injury and increased intracranial pressure in the setting of normal blood pressure. Infusion of dopamine increases cerebral perfusion pressures from 70 mmHg to 90 mmHg leading to decreased intracranial pressure (ICP). Cerebral oxygenation (p_{ti} O_2 , S_{jv} O_2) remains unchanged; cerebral perfusion pressure (CPP), intracranial pressure (ICP), mean arterial pressure (MAP), partial pressure of oxygen in brain tissue (ptiO2), jugular-venous saturation of oxygen (sjvO2).

It has become obvious that monitoring SHI patients involves more than one parameter for clinical decision making. Multiple parameters have to be interpreted in context and their interrelations have to be understood. This is the basis for the so called multiparametric or multimodal cerebral monitoring approach, where all parameters are processed and recorded online. Clinical decisions are driven by direct and/or post-hoc interpretations of a given subset of parameters chosen by the neurointensivist. Detailed retrospective analyses with higher transparency become possible.[3] The first experiences in this field have shown that this is not a trivial challenge and multimodal cerebral monitoring is continuously developing. In Europe, a multicenter initiative has recently been founded by experts in the field ("Brain IT", www.brainit.org).

Therapy

The treatment of severely head injured patients is, as mentioned, mainly the domain of intensive care specialists. However, specific treatment algorithms related to organ pathophysiology, are necessary to meet the demands of this patient group.

Common Concepts of Critical Care

Critical care of SHI aims at maintaining normal physiological balance, i.e. normovolemia, normotension, normothermia and normoglycemia, in these highly-dependent patients.

Normovolemia is guided by the clinical assessment (peripheral edema, pulmonary congestion). Both hypo- and hypertension should be avoided. While the latter is rarely found in acute HI, hypotension is often caused by hemorrhagic shock and needs to be treated accordingly. Substitutes for blood volume are packed red blood cells, colloid solutions like albumin as well as isotonic crystalloids. The use of hypertonic saline has been propagated, especially for fluid resuscitation of patients in shock.[39] Currently experimental and clinical data do not suggest any harm to the injured cerebrum if administered acutely. A profound decrease in ICP is a welcome side effect. Using hypertonic saline as a second-tier therapy for refractory intracranial hypertension has not been tested in a prospective randomized clinical trial yet.[21]

While transient controlled hypothermia decreases cerebral metabolism and ICP, prophylactic and longer-lasting use of hypothermia is discussed controversially. In the *US American National acute brain injury study: hypothermia*, SHI patients were randomized to moderate hypothermia (33° C) for 48 hours or normothermia. No effect on mortality and neurologic outcome was observed. Systemic complications (coagulopathy, pneumonia, sepsis) even led to a worse outcome in the subgroup of patients aged 45 years or older. The subgroup of patients who where hypothermic (<35°C) on admission randomization to the normothermic group also affected outcome adversely.[12,13] Though hypothermia cannot be recommended on the basis of this data, the study supports the common notion that hyperthermia is harmful to the injured brain.[32] Fever caused by infections, which are more commonly observed in head-injured critical care patients, has to be treated promptly (physical, pharmacological, and causal treatment, i.e. antibiotics). The most common nosocomial infection in critical care patients with HI is pneumonia.[72] Its incidence has been progressively lowered during the last years, probably since corticosteroid treatment for HI is no longer favored and because general intensive care is qualitatively better today. Empiric, calculated or targeted antibiotic treatment is indicated based on the degree of suspicion or proof of infection. Hyperglycemia is also less frequently observed in SHI patients since steroid treatment has been abandoned. Disturbances in glucose metabolism, however, do occur and if necessary, insulin is administered to maintain serum glucose at 100–200 mg/dl. Nutritional balance has to be kept in order to respond to the altered requirements of post-injury metabolism. Energy requirements and requirements of other nutritional supplies should be measured and monitored or calculated if possible.

Adequate analgosedation is necessary to avoid stress, pain and fear in SHI patients who are often intubated and ventilated for several days. Sedation also efficiently reduces cerebral metabolism, cerebral blood volume and therefore supports ICP treatment. On the other hand, the need for neurological assessments requires to minimize sedation as much as possible. Commonly, a combination of a benzodiazepine (e.g. midazolam, ˜ 7,0 mg/h or 0,09 mg/

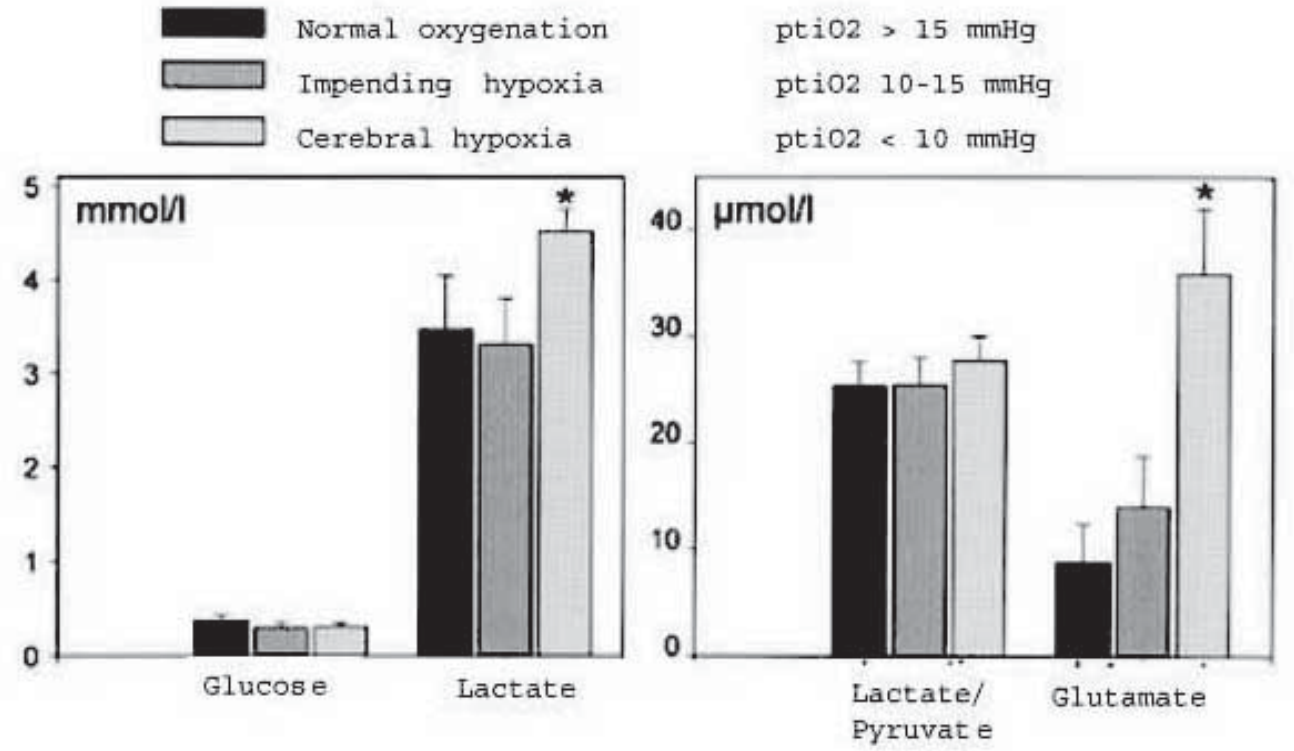

Figure 11. Extracellular cerebral concentrations of intermediary metabolites in severely head injured patients obtained by microdialysis. Note the shift to anaerobic metabolism from the setting of normal tissue oxygenation to impending or manifest cerebral hypoxia (according to Sarrafzadeh et al.[77]); partial pressure of oxygen in brain tissue (ptiO2).

kg/h) and an opioid (e.g. fentanyl, ˜ 0,1 mg/h or 0,0012 mg/kg/h) is used. Individual variations exist and increased ICP eventually makes a higher sedation level desirable. Overall this regimen is relatively well tolerated and both substances can be antagonized if necessary. The risk of seizures with rapid withdrawal have to be kept in mind.

Especially in patients with mild or moderate HI and chronic alcohol abuse, withdrawal can complicate treatment during the first days following injury. In this situation clonidine should be started at a low dose (0,03 mg/h i.v.) to avoid bradycardia, hypotension and oversedation. Increasing doses up to 0.3 mg/h (˜ 0.4 - 4 μg/kg/h) may be necessary individually.

Treatment of Intracranial Hypertension

In the following the specific treatment of HI and increased ICP will be discussed: In **Table 3** principal treatment options, mechanisms and pros and cons are summarized.

Positioning

Both ICP and CPP are significantly affected by positioning of the head. Venous drainage can be reduced if the head is turned sideways, the neck is extended or flexed and jugular veins get torqued or compressed. This in turn can lead to a prompt increase in ICP especially in patients with reduced intracranial compliance. Tight dressings, cervical collars, cervical hematoma, subcutaneous emphysema and high positive endexpiratory pressures are to be avoided.

Elevation of the head and upper torso has been discussed controversially in the past. The dogma that SHI patients have to be positioned in elevation has been disputed by various investigations showing a increased ICP, but constant CPP, CBF and oxygenation in patients with resting flat.[75] As demonstrated in **Figure 12** mild elevation by 15-30° results in an improvement of cerebrovenous return and ICP while CPP and cerebral oxygenation remain constant.[79]

In conclusion, the effect of positioning should not be overestimated in patients with normal or mildly increased ICP.

Ventricular Drainage

As previously discussed ventricular drainage systems can be used for ICP monitoring and therapeutic CSF drainage. Reducing the partial volume of the intracranial CSF spaces compensates for vasocongestion, brain edema, contusional hemorrhages, etc. so that an EVD is a very simple, yet efficient, measure in the treatment of intracranial hypertension. The risk of bacterial contamination and meningitis has to be taken into account.[73]

In principle there are two regimen of CSF drainage: continuous drainage into an external container leveled at a fixed height above the external acoustic meatus, or intermittent drainage at fixed time intervals or whenever a threshold ICP has been reached. For obvious reasons continuous ICP monitoring at the same time is only possible with intermittent drainage or if the ventricular catheter is used along with a second ICP transducer.

Several series have shown that external CSF drainage enables reduction in the intensity of other ICP treatment options (i.e. mannitol, hyperventilation) used in the care of

Therapy	Mechanism	Pros	Cons
Head elevation	venous drainage ↑ CBV↑	simple, efficient	CPP ↓
CSF drainage	intracranial volume↓	simple, efficient	invasive, risk of infection
Hyperventilation: *-Moderate (pCO2 =30mmHg) -Forced (pCO2 <30mmHg)*	vasoconstriction CBV↓, CBF↓	simple, efficient	risk of cerebral ischemia
Osmodiuretics (mannitol)	osmotic gradient, "dehydration" of the brain, improved rheology	simple	nephrotoxicity (keep plasma osmolarity <320 mosmol)
Barbiturates	metabolism ↓, CBF ↓, CBV↓		EEG monitoring necessary, MAP ↓, risk of pulmonary infection
THAM	vasoconstriction, buffering		cerebral oxygenation ↓
Surgical decompression (+duroplasty)	Intracranial space ↑		risk of operation
Hypothermia	metabolism ↓, CBF ↓, CBV ↓		technically difficult, systemic side effects

Table 3. Treatment options for intracranial hypertension; cerebral blood flow (CBF), cerebral blood volume (CBV), cerebral perfusion pressure (CPP), cerebrospinal fluid (CSF), electroencephalography (EEG), mean arterial pressure (MAP), tris buffer (THAM)

SHI patients.[30]

Hyperventilation

Cerebral vasoconstriction is the physiological mechanism of hyperventilation on ICP. Moderate and forced hyperventilation have to be differentiated (pCO_2 30–35 mmHg and pCO_2 <30 mmHg, respectively). As demonstrated in **Figures 13 and 14**, hyperventilation diminishes ICP rapidly. On the other hand undue vasoconstriction increases the risk of secondary ischemic injuries.[19,70]

In a controlled clinical trial, the clinical outcome of patients with SHI was adversely affected by prolonged forced hyperventilation (pCO_2 ~ 25 mmHg). In clinical practice, prophylactic hyperventilation has therefore been abandoned.[68]

Transient hyperventilation, although efficiently reducing the ICP and improving CPP, is always associated with a decrease in cerebral oxygenation. Critically impaired oxygenation, however, occurs with forced hyperventilation only.[50]

Currently it is recommended to use hyperventilation transiently for instances of acute neurological deterioration or long-term whenever intracranial hypertension is refractory to sedation, CSF drainage and osmodiuretic treat- ment. Forced hyperventilation should only be used if continuous surveillance of cerebral oxygenation is feasible.[7]

Osmodiuretics (Mannitol)

Intracranial pressure can be efficiently lowered with osmodiuretics. Typically mannitol (20%, i.v.), sorbitol (40%, i.v.) or glycerol (10%, i.v./p.o.) is administered. Currently most clinicians in neurointensive care prefer mannitol (20%). In adults approximately 125 ml (i.e. 0.3[–1.0] g/kg) are infused as a bolus over 10–20 minutes. If a more profound reduction of ICP is necessary, e.g. intraoperatively, up to 250 ml can be given. Higher doses have been suggested for pre-operative use whenever patients have clinical signs of impending herniation and some time is required for Operation Room transfer.[17] Future investigations will show if hypertonic saline could be a potential substitute if osmodiuretics are contraindicated because of hypovolemia and/or hypotension.[21]

Routine use in patients with increased ICP is either intermittently scheduled (e.g. every eight hours) or whenever ICP reaches a defined threshold. Most clinicians prefer the former mode, where mannitol boluses are scheduled every 8, 6, 4 or even 2 hours. Administered two-hourly a daily dose of 4 g/kg is reached. With repeated boluses, mannitol can cumulate and therefore plasma osmolality has to be checked before continuing osmotherapy. Plasma osmolalities beyond 320 mosmol/l carry the risk of nephrotoxicity and acute tubular necrosis.

There are at least two mechanisms which are

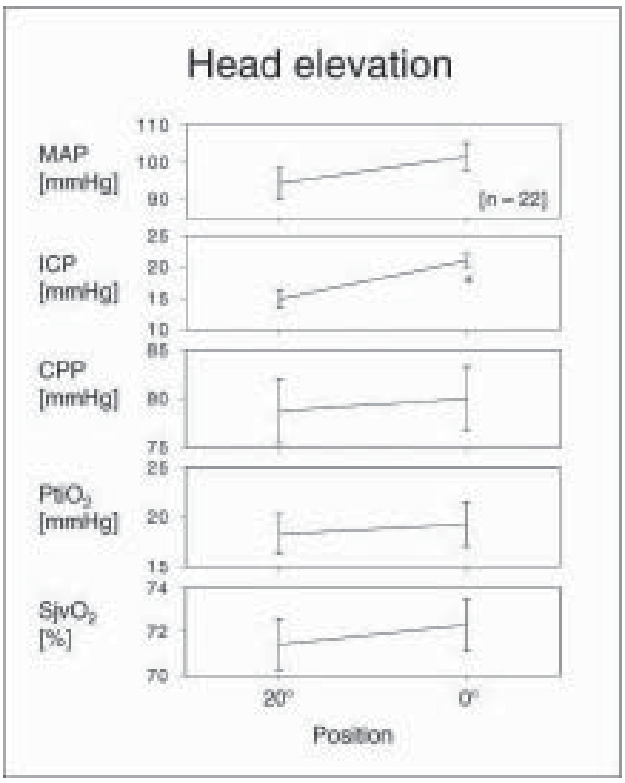

Figure 12. Effect of altering head position from mild elevation to the supine position in severely head-injured patients. Both intracranial pressure and mean arterial pressure increase, resulting in unchanged cerebral perfusion pressure and oxygenation; cerebral perfusion pressure (CPP), intracranial pressure (ICP), mean arterial pressure (MAP), partial pressure of oxygen in brain tissue (ptiO2), jugular-venous saturation of oxygen (sjvO2).

complementary in the use of mannitol: increasing the osmolar gradient of plasma and cerebral interstitium transiently leads to an unspecific "dehydration" of well-perfused tissue. Additionally hemorheology is improved acutely leading to enhanced cerebral perfusion **(Figure 15)**.[4,43,64]

Rebound phenomena have been postulated to occur in patients with breakdown of the blood brain barrier (BBB). Then mannitol is thought to transit into the cerebral parenchyma and bind water locally. Therefore accumulation over time could theoretically lead to increased ICP. So far neither has the rebound phenomenon been proven, nor has it been dismissed. Both clinical and experimental experience, however, demonstrates that patients with contusions (and proven BBB breakdown) can be treated with mannitol over several days without adverse effects on ICP.[92] With prolonged osmodiuretic treatment strict charting of fluid intake and output is necessary to avoid hypovolemia.

Barbiturate coma

Barbiturate coma is known to effectively lower cerebral metabolism which is coupled with cerebral perfusion and consecutively with decreased cerebral blood volume. Therefore ICP is affected beneficially **(Figure 16).** Further (wanted) properties are its anticonvulsive activity, reduced liberation of free oxygen radicals, inhibition of lysosomal enzymes, and moderate reduction of the core temperature.[56] Unwanted side effects are due to systemic vasodilation (hypotension), leukocyte depression (infections) and sequelae as severe as sepsis and adult respiratory distress syndrome (ARDS). Hepatotoxicity can complicate treatment and, in the worst case, lead to acute liver failure. To avoid overdosage barbiturate coma should be monitored by electroencephalography (EEG) where a "burst suppression pattern" is contemplated.[93]

To predict the effect of barbiturate therapy individually, a test dose of 5 mg/kg thiopental should be infused over 30 minutes. Continued barbiturate coma is not reasonable if CPP decreases.[22] A maintenance dose of 5 mg/kg/h is recommended, but therapeutic serum levels vary individually. Therefore continuous EEG monitoring is necessary to titrate exactly to the therapeutic goal where the effect of thiopental on cerebral metabolism is maximal (i.e. burst suppression).[93]

According to the AANS guidelines barbiturate coma is a "second-tier" therapy that should be used after CSF-drainage, moderate hyperventilation and osmotherapy. Following several prospective, randomized clinical trials the prophylactic use of barbiturates is obsolete nowadays.[80,93]

Tris Buffer

Intravenous application of tris buffer (THAM) leads to a significant reduction in ICP. The exact mechanism is still

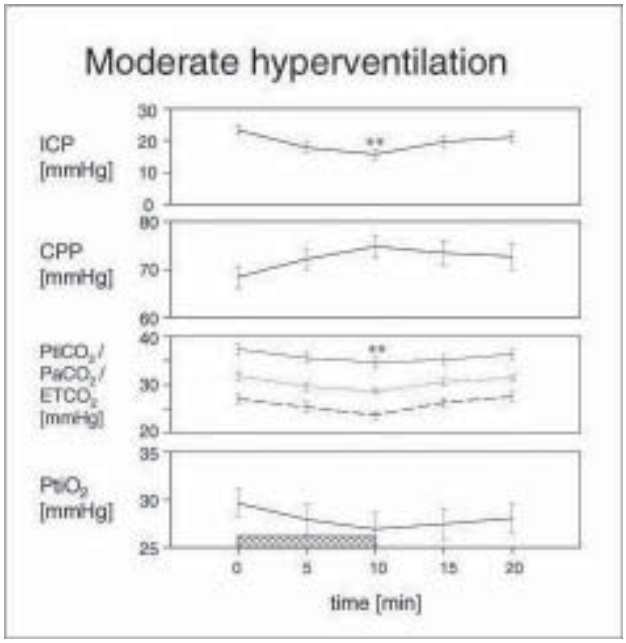

Figure 13. Moderate hyperventilation over 10 minutes leads to hypocapnia (30 mmHg) in severely head-injured patients. Accordingly, intracranial pressure decreases at the cost of lower cerebral oxygenation, however. Parameters normalize after 10 minutes of normoventilation; cerebral perfusion pressure (CPP), endtidal partial pressure of carbondioxide (ETCO2), intracranial pressure (ICP), mean arterial pressure (MAP), partial pressure of oxygen in brain tissue (ptiO2), partial pressure of carbondioxide in brain tissue (ptiCO2).

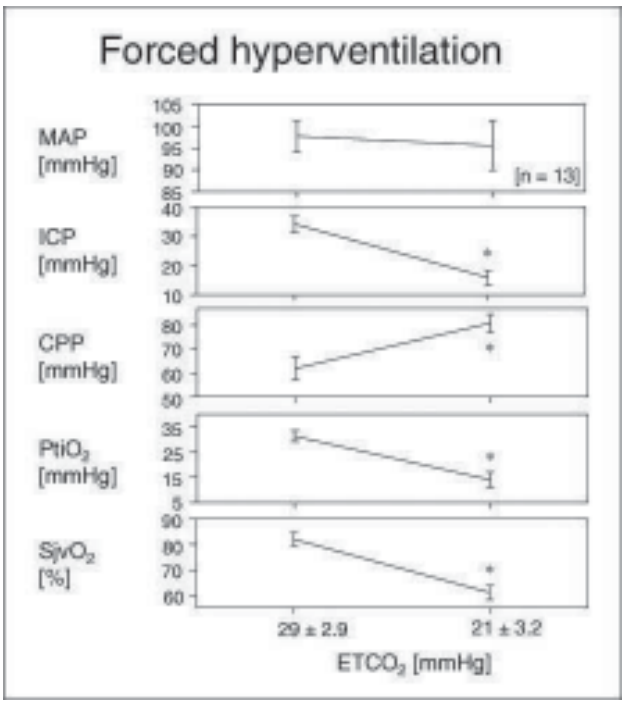

Figure 14. Forced hyperventilation with an end-tidal partial pressure of carbondioxide (ETCO2) decreased to about 20 mmHg leads to significantly decreased intracranial pressure in severely head-injured patients. Cerebral oxygenation, however, drops critically with this maneuver; cerebral perfusion pressure (CPP), endtidal partial pressure of carbondioxide (ETCO2), intracranial pressure (ICP), mean arterial pressure (MAP), partial pressure of oxygen in brain tissue (ptiO2), jugular-venous saturation of oxygen (sjvO2).

not fully understood, but is postulated to buffer intracellular acidosis and act as a diuretic. Several experimental studies have shown beneficial effects of THAM in cerebral lesions, e.g. improvement of intra- and extracellular acidosis, reduction of tissue lactate concentrations, perifocal edema and infarct volume in ischemic stroke, and significant decrease in posttraumatic edema and normalization of cellular energy metabolism in traumatic lesions.[1,25] In a prospective randomized clinical trial THAM was used as a continuous infusion either with prolonged hyperventilation or as stand alone treatment for increased ICP in SHI patients.[68] Combination treatment lead to a cancellation of negative effects associated with prolonged hyperventilation, whereas stand alone treatment did not improve clinical outcome compared to the control group.[68] Bolus infusion of THAM can be used to treat increased ICP acutely. At a dose of 1 mmol/kg a reduction in ICP and improvement in CPP can be achieved, which is associated, however, with a significant reduction in arterial and cerebral tissue oxygenation (**Figure 17**). Routine use of THAM in the treatment of increased ICP is therefore obsolete.[48]

Catecholamines

Catecholamines are used in the core concept of CPP management.[76] As outlined earlier, CPP management remains under debate, especially since intact cerebral autoregulation is presumed, which is not always the case under pathologic conditions.

The treatment of intracranial hypertension should therefore aim at reducing ICP through first-line measures like moderate hyperventilation, CSF drainage and osmodiuretics. If ICP remains high albeit these measures, catecholamines can be introduced under continuous monitoring of ICP, MAP and CPP. Normovolemia should be maintained and kidney function monitored thoroughly.[88]

Decompressive Hemicraniectomy (With Duroplasty)

Decompressive hemicraniectomy with duraplasty has seen a *renaissance* in neurosurgery over the past decade. In earlier times epidural and subdural hematomas where removed without reimplanting bone flaps acutely. This procedure (even with extended size and with duraplasty) has not yielded better clinical results compared to acute reimplantation.

Decompressive hemicraniectomy nowadays means a secondary intervention if conservative treatment of posttraumatic brain swelling fails and intracranial hypertension necessitates "second-tier" treatment. Surgical decompression can be carried out uni- or bilaterally,

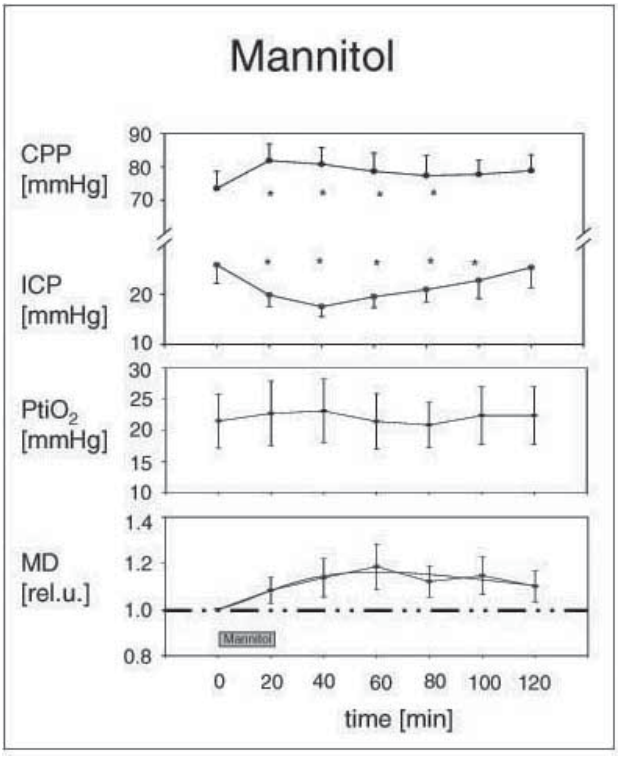

Figure 15. In severely head-injured patients mannitol bolus (0.3 g/kg administered over 20 minutes) produce an unpecific increase in extracellular concentrations of glucose, lactate, pyruvate and glutamate (here subsumed as low-molecular metabolites measured by microdialysis).Despite significant improvement in intracranial pressure and cerebral perfusion pressure no specific change in cerebral oxygenation and energy metabolism occurs. Intracranial hypertension prior to intervention is only mild, however; cerebral perfusion pressure (CPP), intracranial pressure (ICP), microdialysis (MD), partial pressure of oxygen in brain tissue (ptiO2).

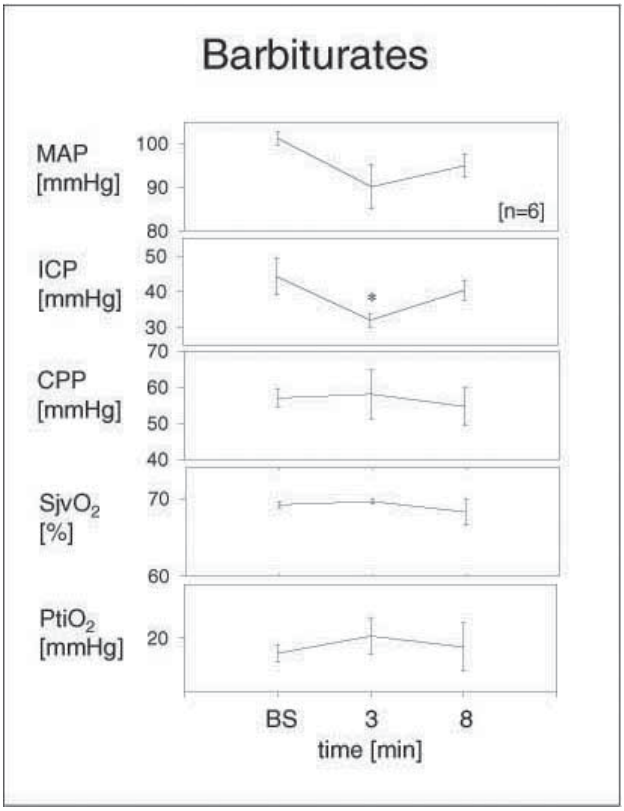

Figure 16. Barbiturate coma (thiopental, 500mg bolus) decreases intracranial pressure significantly in severely head-injured patients. Blood pressure, however, is also reduced, so that cerebral perfusion pressure remains unchanged. Cerebral oxygenation is unaffected by this maneuver; cerebral perfusion pressure (CPP), intracranial pressure (ICP), mean arterial pressure (MAP), partial pressure of oxygen in brain tissue (ptiO2), jugular-venous saturation of oxygen (sjvO2).

fronto-temporo-parietally or bifrontally. **Figure 18** demonstrates exemplarily how decompressive hemicraniectomy decreases ICP, increases CPP and augments / stabilizes cerebral oxygenation.

Especially young patients without primary pupillary dysfunction and brainstem injuries seem to benefit most from this treatment. A recent prospective study has shown a favorable outcome in 58% of all patients in this subgroup.[35] In patients above the age of 50 decompressive hemicraniectomy does not improve outcome significantly.[78] In patients with severe hypoxic cerebral injuries this treatment is not indicated.

Hypothermia

Moderate hypothermia (˜32°C core temperature) is a physical measure to lower ICP. Hypothermia reduces cerebral metabolism, CBF and CBV. Insofar the mechanism is very similar to barbiturate coma. Adverse effects of moderate hypothermia have been described on coagulation, liver, pancreas and kidney function.[65]

As shown by the recent multicenter trials in the US, prolonged moderate hypothermia does not improve mortality and clinical outcome in SHI patients.[12,13] A new trial to assess a potential benefit in a subgroup of patients (hypothermic on arrival, age 16–45) has started enrollment in 2002.

Treatment Algorithm for Intracranial Hypertension

Based on aforementioned measures, treatment pathways for intracranial hypertension have been developed. The decision tree in **Figure 19** closely resembles recommendations of the AANS guidelines.[6,7]

These are oriented on treatment thresholds for ICP/ CPP of 20 and 60 mmHg, respectively. First line measures (sedation, positioning, ventriculostomy, osmotherapy, moderate hyperventilation) have to be differentiated from so-called "second-tier" therapies (e.g. barbiturate coma, decompressive hemicraniectomy).

Cerebral oxygenation measurements ($S_{jv}O_2$ or $p_{ti}O_2$) have not become clinical standard yet, but are recommended for use with forced hyperventilation (a second-tier therapy).

Pharmacotherapy

Glucocorticosteroids

In the 60s of the last century glucocorticosteroids were introduced in the treatment of peritumoral brain edema. The mechanisms are manifold: vascular permeability is

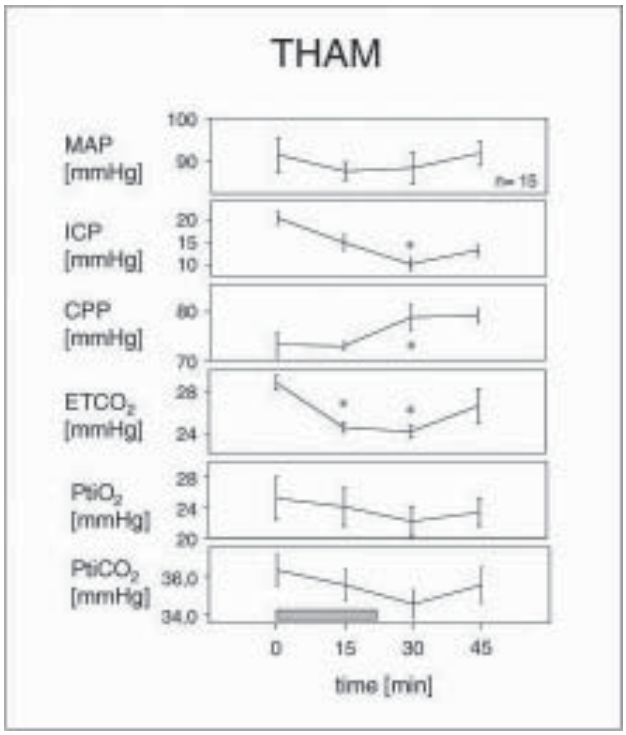

Figure 17. In severely head-injured patients tris buffer (THAM, 1 mmol/kg bolus administered over 20 minutes) leads to a reduction of intracranial pressure and improved cerebral perfusion pressure. Tissue oxygenation, however, is impaired by this maneuver; cerebral perfusion pressure (CPP), endtidal partial pressure of carbondioxide (ETCO2), intracranial pressure (ICP), mean arterial pressure (MAP), partial pressure of oxygen in brain tissue (ptiO2), partial pressure of carbondioxide in brain tissue (ptiCO2), tris buffer (THAM).

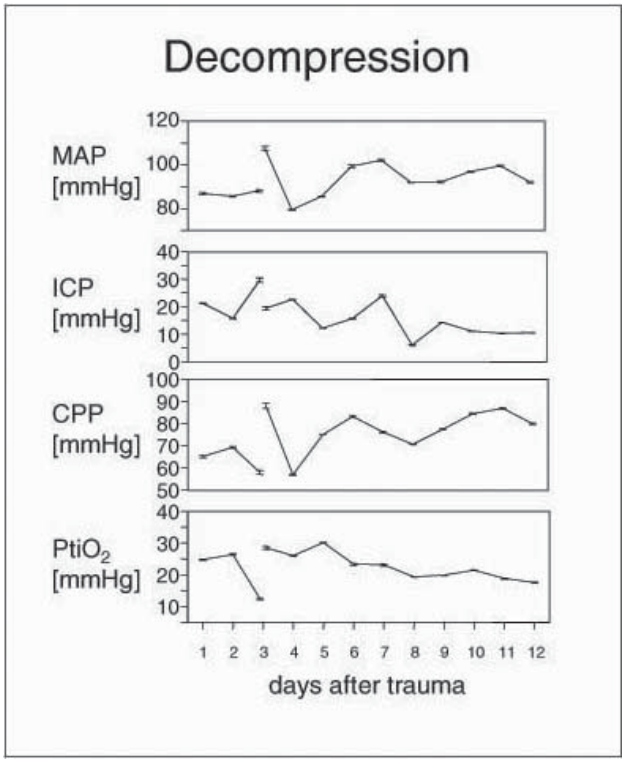

Figure 18. Example of decompressive hemicraniectomy and duraplasty in a severely head-injured patient on the third day after trauma. Sustained reduction in intracranial pressure, improved cerebral perfusion pressure and oxygenation is achieved. Surgery was indicated after conservative treatment of increased intracranial pressure had failed and cerebral perfusion pressure could not be held above 60 mmHg; cerebral perfusion pressure (CPP), intracranial pressure (ICP), mean arterial pressure (MAP), partial pressure of oxygen in brain tissue (ptiO2).

reduced in and surrounding brain tumors, CSF production is down-regulated, generation of free radicals and calcium influx into neurons and glia are reduced. All these mechanisms could potentially be neuroprotective in traumatic lesions as well. In a number of experimental studies beneficial effects of administering steroids following trauma have been demonstrated. Trials to reproduce these effects clinically have failed, however.[3,24] The prospectively-lead, double-blind and randomized trial by Braakman and Dearden in particular has been frequently cited as an evidence-based argument against a general use of steroid in TBI.[5,20]

More recently, however, experimental findings have raised hope that ultra-high steroid dosages may be neuroprotective indeed. Based on this assumption two multicentric, prospective randomized clinical trials have been conducted. One of them remained inconclusive, since outcome in the control arm was better than expected and no difference to the treatment arm was found.[26] The second study also failed to show any benefit overall, but subgroup analysis revealed a significant improvement in the clinical outcome of patients with focal contusions.[33]

The most recent international study (CRASH, "Corticosteroid Randomization After Significant Head injury") has been stopped after more than 10 thousand patient enrollments. High dose methylprednisolone treatment over 48 hours had led to a significantly higher mortality at 2 weeks following trauma in the treatment arm.[16]

In summary, the use of steroids is not recommended for the treatment of patients following TBI.

Aminosteroids

Aminosteroids are more potent inhibitors of lipid peroxidation than glucocorticosteroids. They lack other glucocorticoid properties, but inhibit the generation of free radicals, slow-down endogenous vitamin E degradation, etc. Experimentally many aminosteroids have shown neuroprotective effects.[37] Clinically the aminosteroid tirilazade mesylate has, therefore, been tested in the treatment of cerebral vasospasm following aneurysmal subarachnoid hemorrhage and in TBI. While at least in male patients with high-grade SAH there was a statistically significant benefit, both multicentric studies on patients with TBI have failed to show any advantage over placebo. In the US American study the outcome of patients treated with tirilazade was even worse compared to placebo, possibly confounded, however, by a higher incidence of posttraumatic hypotension and hypoxia.[61]

Overall, aminosteroids are not recommended for use in patients following TBI.

Calcium Antagonists

The mechanism of nimodipine, which has been in the focus of calcium antagonist studies, is a reduction of calcium influx in neurons injured by hypoxia or ischemia. Relaxation of smooth muscle cells and inhibition of vasospasm has been hypothesized as a mechanism of action in subarachnoid hemorrhage (SAH), but neither does it prevent or ameliorate vasospastic vessel narrowing in itself nor does it improve CBF.

The data available for use of nimodipine in TBI is more complex, however. Two large multicenter studies failed to prove an effect of nimodipine in patients with SHI.[42,46,83] Accordingly the general use of calcium antagonist in SHI patients is not recommended. Yet, subgroup analyses have indicated a positive effect in patients with traumatic SAH.[46] Assuming efficacy in this group of patients a multicentric study has been carried out in Germany. Although a significant effect on clinical outcome was found, several points of critique regarding methodology have been raised afterwards.[38] In conclusion a fourth trial has been conducted, which has also failed to show a benefit. A comprehensive publication of results is still pending.

More and more evidence has been gathered that traumatic SAH is an important prognosticator in SHI.[87] This has possibly been misjudged in the past, as the occurrence of traumatic "vasospasm" has been underestimated. Significant vasospasm following traumatic SAH has a lower incidence (10%) when compared to aneurysmal SAH. Some of the pathomechanisms may be shared however, and it remains to be tested if similar treatment strategies (i.e. hemodynamic therapy) can be applied. One of the main problems is the accurate diagnosis

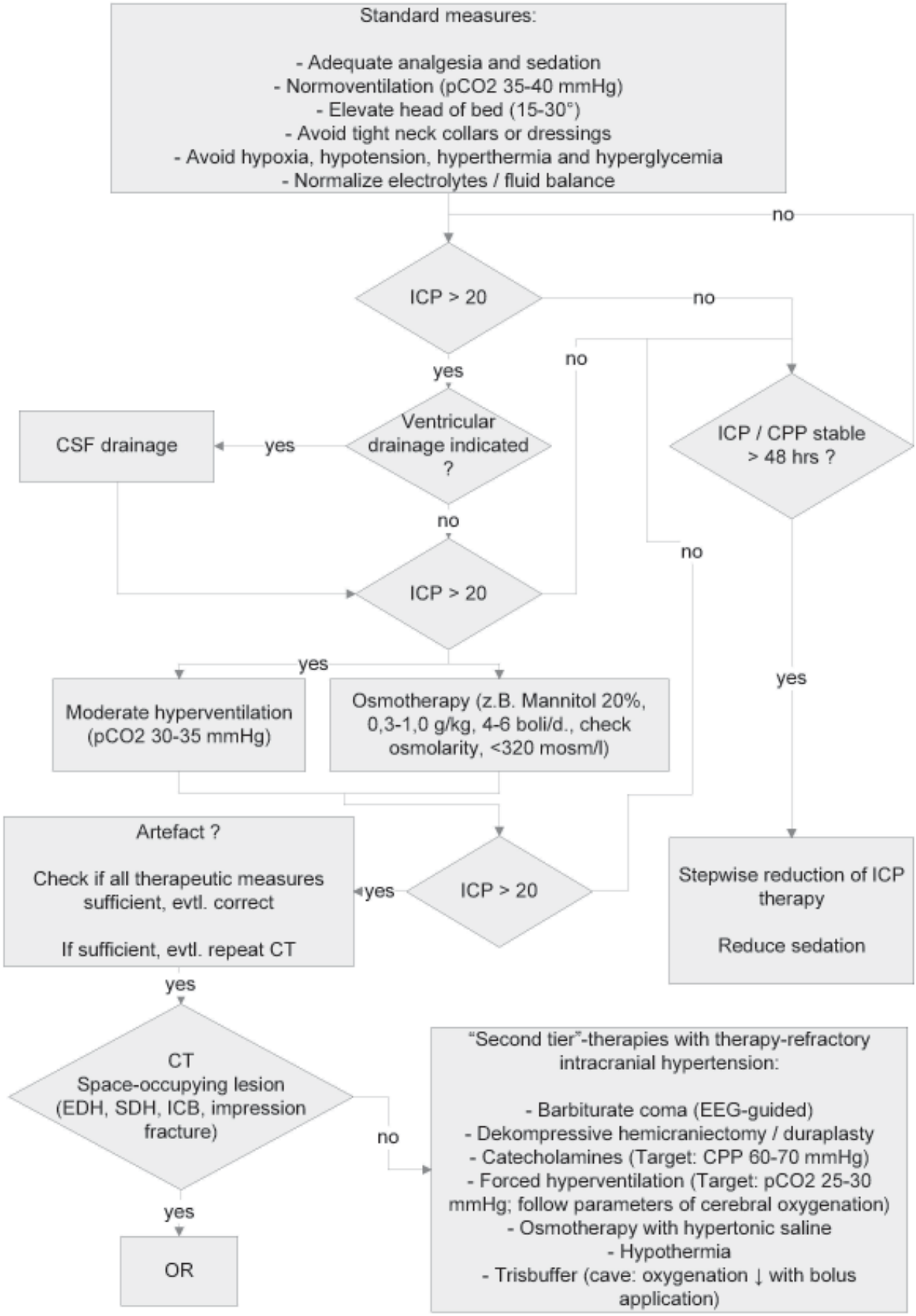

Figure 19. Treatment algorithm for intracranial hypertension (following AANS-guidelines and recommendations of the EBIC[7,57]); cerebral perfusion pressure (CPP), cerebrospinal fluid (CSF), epidural hematoma (EDH), electroencephalography (EEG), intracerebral hematoma (ICH), intracranial pressure (ICP), Operating room (OR), subdural hematoma (SDH).

of traumatic "vasospasm" since the value of transcranial Doppler sonography in the detection of vasospastic vessel narrowing is controversial in any respect.

In summary, calcium antagonists like nimodipine might have an indication in the treatment of patients with TBI and traumatic SAH. More comprehensive trials will be necessary for a clear recommendation, however.

Glutamate-(NMDA-) Receptor Antagonists.

Glutamate is an important biochemical factor in the development of secondary injuries following ischemia and trauma. Therefore glutamate receptor antagonists have been on the frontline of experimental and clinical testing.[69] In several experimental studies beneficial effects of glutamate receptor antagonists have been demonstrated and a number of agents have even been tested clinically (phase II and III). Similar to the disappointing results in stroke research, no agent improving the outcome of patients with TBI has been tested yet. Two SHI studies on the use of Selfotel™ and one study on the non-competitive antagonist Cerestat™ (aptiganel) have been discontinued with unsatisfactory interim results. Other studies utilizing the glutamate antagonists D-CPPene, CP 101-606 and Eliprodil have been conducted without positive result. Dexanabinol, a synthetic analog of the active component of marijuana is a non-competitive inhibitor on NMDA-receptors, as well as a free radical scavenger and antioxidant. A recently concluded phase-II-trial has demonstrated a positive effect on ICP and CPP. However, this has not been reflected in clinical outcome so far.[51] Results of the recently concluded phase-III-trial are pending.

At this time, glutamate receptor antagonists cannot be recommended for neuroprotective treatment of patients following TBI.

Anticonvulsants

Posttraumatic seizures affect a high percentage of SHI patients especially those with focal lesions (i.e. contusions). The incidence has been reported between 5 and 40%, reflecting uncertainties in the diagnosis. Early posttraumatic seizures (within 7 days after trauma) have to be differentiated from late posttraumatic seizures. Anticonvulsants like phenytoin and carbamazepine do reduce the incidence of early posttraumatic seizures significantly when given prophylactically. The occurrence of late posttraumatic seizures and the clinical outcome are unaffected, however.[7,85] Therefore prophylactic treatment is generally not recommended (standard), but, according to the US-American guidelines, can be used optionally to prevent early post-traumatic seizures in patients at high risk (e.g. with cortical lesions).[7]

It has to be underscored that these recommendations apply to *prophylactic* use, while anticonvulsant treatment should certainly be initiated with proven occurrence of posttraumatic seizures.

Implications for the Nepalese Healthcare System

Contemporary management strategies for TBI can not immediately be applied to Nepalese healthcare. Effective management of head injured persons in Nepal is hindered by a difficult geographical location, unavailability of trained personnel in the field and difficulty in transporting the patients due to lack of motorable roads. While some of the equipment for the treatment of TBI victims is readily available (e.g. ventricular drainage), others are scarce(e.g. operating room capacity, ICU beds) or completely unavailable (e.g. EMS providers, specialized monitoring equipment).

Though the number of clinicians interested in neurotrauma care has increased over the last 10 years (one neurosurgeon in 1989 to 10 in 2004, and some general surgeons in the regional centers doing basic craniotomies and burrholes), this has not been able to translate into any recognizable inprovement in the overall neurosurgical care in the national perspective. The following steps, however, are suggested to improve the situation for head injury patients:

1. The concept of EMS is virtually nonexistent in Nepal. Patients are frequently evacuated from the scene by bystanders or police personnel and taken to the nearby healthcare facility which can sometimes take several days as availability of ambulances is restricted to big cities only. Establishment of EMS systems would probably be a key step in improving care for head-injured patients, as hypoxia and hypotension in the field are well-known, yet avoidable, "killers" in TBI victims.
2. Establishment of regional trauma centers with basic 3-6 months condensed and intensive training of general surgeons in trauma neurosurgery. Simple, yet efficient, treatment options like ventricular drainage systems should be made available at every trauma hospital. At the same time, these would allow ICP/CPP-directed treatment by properly trained personnel.
3. Awareness campaign about the seriousness of head trauma to the general public. Recent introduction of helmet laws for motorcyclists and mandatory seat belts for drivers and front seat passengers of motor vehicles are first steps. A program similar to "Think First" in the US would be a cost-effective measure of primary prevention.
4. Prioritizing the neurotrauma care from the existing health institutions from the country. Timely intervention of people with neurotrauma is frequently delayed even in the tertiary care facility. Epidural hematomas occasionally have to compete with, for example, Caesarian sections or gut perforations as only one emergency OR is available in many centers in Nepal providing neurotrauma care. Training of anesthesiologists in neuroanesthesia is also needed. Along with this, availability of dedicated neuro ICUs (at this time almost non-existent in the country) would convert many "deaths" and "vegetative states" into "good outcomes".
5. Currently no rehabilitation centers for head trauma patients exist in Nepal. Time has come for the

government and the private sectors to think of setting up one, as rehabilitation often has a significant impact on the ultimate recovery.

6. Finally, establishment of rigorous neurosurgery training programs tailored to the country's situation is urgently needed to make neurosurgery services sustainable and available at a reasonable cost to all people.

Regrettably, the situation of care for neurotrauma patients in Nepal does not seem be promissing in the foreseeable future. The ongoing civil unrest has crippled life in many parts of the country which, in turn, has affected the care of patients in every aspect of care right from injury prevention to tertiary care.

Despite this cumbersome environment, the very first steps of improvement have already been taken by local pioneers in the field. Continuing support by the international neurosurgical community is encouraged.

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