Seit > 5 Jahren nicht aktualisiert, Leitlinie wird zur Zeit überarbeitet

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LEITLINIE SCHÄDELHIRNTRAUMA IM ERWACHSENENALTER

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Synonyme: Schädelhirnverletzung

ICD 10-GM Version 2014 (Auszug der wichtigsten Schlüssel):

S06.-	**Intrakranielle Verletzung** Benutze die zusätzliche Schlüsselnummer S01.83 (Offene Wunde mit Verbindung zu einer intrakraniellen Verletzung) zusammen mit S06, um eine offene intrakranielle Verletzung zu verschlüsseln. Bei den Subkategorien S06.0-S06.9 ist ein Bewusstseinsverlust mit einer zusätzlichen Schlüsselnummer aus S06.7 zu verschlüsseln.
S06.0	**Gehirnerschütterung** Commotio cerebri
S06.1	**Traumatisches Hirnödem**
S06.2-	**Diffuse Hirnverletzung** Großer Hirngewebebereich betroffen
S06.20	Diffuse Hirn- und Kleinhirnverletzung, nicht näher bezeichnet
S06.21	Diffuse Hirnkontusionen - Bis zu 5 ml Blut
S06.22	Diffuse Kleinhirnkontusionen - Bis zu 5 ml Blut
S06.23	Multiple intrazerebrale and zerebelläre Hämatome - Mehr als 5 ml Blut Multiple intrazerebrale Blutungen
S06.28	Sonstige diffuse Hirn- und Kleinhirnverletzungen Multiple Rissverletzungen des Groß- und Kleinhirns
S06.3-	**Umschriebene Hirnverletzung** Begrenzter oder umschriebener Hirngewebebereich betroffen
S06.30	Umschriebene Hirn- und Kleinhirnverletzung, nicht näher bezeichnet
S06.31	Umschriebene Hirnkontusion - Bis zu 5 ml Blut
S06.32	Umschriebene Kleinhirnkontusion - Bis zu 5 ml Blut

S06.33	Umschriebenes zerebrales Hämatom - Mehr als 5 ml Blut Intrazerebrale Blutung/Intrazerebrales Hämatom
S06.34	Umschriebenes zerebelläres Hämatom - Mehr als 5 ml Blut Kleinhirnblutung/Zerebelläre Blutung
S06.38	Sonstige umschriebene Hirn- und Kleinhirnverletzungen Rissverletzung des Groß- und Kleinhirns
S06.4	**Epidurale Blutung** Epidurales [extradurales] Hämatom/Extradurale Blutung (traumatisch)
S06.5	**Traumatische subdurale Blutung**
S06.6	**Traumatische subarachnoidale Blutung**
S06.7-!	**Bewusstlosigkeit bei Schädelhirntrauma**
S06.70!	Weniger als 30 Minuten
S06.71!	30 Minuten bis 24 Stunden
S06.72!	Mehr als 24 Stunden, mit Rückkehr zum vorher bestehenden Bewusstseinsgrad
S06.73!	Mehr als 24 Stunden, ohne Rückkehr zum vorher bestehenden Bewusstseinsgrad
S06.79!	Dauer nicht näher bezeichnet
S06.8	**Sonstige intrakranielle Verletzungen** Traumatische Blutung, traumatisches Hämatom, Kontusion: intrakraniell o. n. A./Kleinhirn
S06.9	**Intrakranielle Verletzung, nicht näher bezeichnet** Hirnstammverletzung o. n. A./Hirnverletzung o. n. A./Intrakranielle Verletzung o. n. A.
T90.5	**Liquorfistel als Folge einer intrakraniellen Verletzung** (Nur als Nebendiagnose zusätzlich zu einem Code aus S06.-)

Tabelle 1: Verwandte Abkürzungen

ABC	ABC-Regel: Airways, Breathing, Circulation – Atemwege freihalten, Beatmung, Zirkulation (Kreislauf) prüfen u. ggf. in Gang bringen
CT	Computertomographie, Computertomogramm
ICD10 GM	International classification of diseases - Version 10, German modification
ICP	Intracranial pressure – Intrakranieller Druck/Hirndruck
CPP	Cerebral perfusion pressure – zerebraler Perfusionsdruck
GCS	Glasgow Coma Scale, Glasgow Coma Score
MR, MRT	Magnetresonanztomographie
SHT	Schädelhirntrauma

1. EINLEITUNG:

Schädelhirnverletzungen, bedeutungsgleich mit Schädelhirntraumata, sind bis zum frühen Erwachsenenalter die häufigste Todesursache [Jennett 1991]. Hirngewebe hat die geringste Sauerstoffmangeltoleranz aller Organe, die Rechtzeitigkeit der Behandlung ist daher häufig entscheidend für das Überleben bzw. das Ausmaß der bleibenden Behinderung des Verletzten. Die Leitlinie soll die derzeit aktuellen Methoden in der Diagnostik und Therapie dieses Krankheitsbildes am Unfallort, auf dem Transport und im Krankenhaus darstellen.

Die Leitlinie richtet sich daher an die in der Versorgung schädelhirnverletzter Patienten tätigen Gesundheitsberufe. Zum Verständnis dieser Leitlinie sind medizinische Vorkenntnisse erforderlich. Neben dieser Langversion sind eine **Kurzversion** und eine **Patienten-/Angehörigenversion** verfügbar. Die Entstehung der Leitlinie wird in einem gesondert publizierten **Leitlinienreport** beschrieben.

Grundlage dieser Leitlinie ist die Evidenz (d. h. die Nachweisstärke der Effektivität) der in der wissenschaftlichen Literatur publizierten Daten, die in fünf Stufen eingeteilt wird (Oxford Center of Evidence based Medicine, 2009). Auf der Basis der Evidenzgrade der einzelnen Aussagen erfolgt im Leitlinienentwicklungsprozess die Festlegung der **Empfehlungsgrade A, B** oder **0** gemäß den Empfehlungen des Nationalen Programms für die Versorgungsleitlinien [NVL 2008].

Die **Empfehlungsgrade A, B, 0** bedeuten:

Tabelle 1: Empfehlungsgrade gemäß NVL

KÜRZEL	BESCHREIBUNG	FORMULIERUNG IN EMPFEHLUNG	
A	Starke Empfehlung	Soll…	soll nicht…
B	Empfehlung	Sollte…	sollte nicht…
0	Empfehlung offen	Kann…	kann verzichtet werden…

Über die Einstufung wurde innerhalb der Leitlinienentwicklungsgruppe ein Konsens hergestellt. Es kam vor, dass im Einzelfall bei der Festlegung des Empfehlungsgrades von dem Evidenzgrad abgewichen wurde. Aufgrund jahrzehntelanger, übereinstimmender Erfahrungen wurden darüber hinaus auch einige Maßnahmen, wie die operative Versorgung raumfordernder intrakranieller Blutungen, mit einem hohen Empfehlungsgrad versehen, auch wenn hierfür keine Studien vorliegen. Diese Empfehlungen sind Ausdruck allgemein anerkannter guter klinischer Praxis, die nicht in Frage gestellt wird. Im Allgemeinen resultieren die Empfehlungsgrade jedoch aus folgenden Evidenzgraden (Oxford Center of Evidence based Medicine, 2009).

Therapiestudien:

Empfehlungsgrad	Evidenzgrad	Studien-/Literaturtyp
A	**1a**	Systematischer Review randomisierter kontrollierter Studien.
	1b	Mindestens eine randomisierte kontrollierte Studie (RCT)
B	**2a-b**	Systematischer Review von vergleichenden Kohortenstudien
	3a-b	Systematischer Review von Fall-Kontrollstudien oder mindestens eine gut geplante kontrollierte Studie
0	**4**	Fallserien und mangelhafte Fall-Kontrollstudien, begründete Expertenmeinung
	5	Meinungen ohne explizite kritische Bewertung

Diagnosestudien:

Empfehlungsgrad	Evidenzgrad	Studien-/Literaturtyp
A	**1a**	Systematischer Review guter Diagnose-Studien vom Typ Ib
	1b	Studie an einer Stichprobe der Zielpopulation, bei der bei allen Patienten der Referenztest unabhängig, blind und objektiv eingesetzt wurde
B	**2a-b**	Systematischer Review von Diagnosestudien oder mindestens eine, bei der an einer selektierten Stichprobe der Zielpopulation der Referenztest unabhängig, blind und objektiv eingesetzt wurde
	3a-b	Systematischer Review von Diagnosestudien oder mindestens eine, bei der der Referenztest nicht bei allen Personen eingesetzt wurde
0	**4**	Fall-Kontrollstudie oder Studien mit nicht unabhängig, blind oder objektiv eingesetztem Referenztest
	5	Meinungen ohne explizite kritische Bewertung

2. DEFINITION:

Ein **Schädelhirntrauma** ist Folge einer Gewalteinwirkung, die zu einer Funktionsstörung und/oder Verletzung des Gehirns geführt hat und mit einer Prellung oder Verletzung der Kopfschwarte, des knöchernen Schädels, der Gefäße und/oder der Dura verbunden sein kann. Eine Verletzung des Kopfes ohne Hirnfunktionsstörung oder Verletzung des Gehirns bezeichnet man als **Schädelprellung**.

Falls die Dura bei gleichzeitiger Verletzung der Weichteile und des Knochens zerrissen ist und somit eine Verbindung des Schädelinneren mit der Außenwelt besteht, so liegt ein **offenes SHT** vor.

Primärer und sekundärer Hirnschaden. Zu unterscheiden ist zwischen einer primären und sekundären Läsion. Unter **primär** wird die im Augenblick der Gewalteinwirkung entstehende Schädigung des Hirngewebes verstanden. Diese Primärläsion umfasst irreversibel zerstörte Zellen einerseits und funktionsgestörte Neurone andererseits, die aber prinzipiell überleben und regenerieren können. Die primäre Schädigung ist Ausgangspunkt für eine Kaskade von Reaktionen, die die primäre Verletzungsfolge verstärkt. Diese **Sekundärläsion** kann gegebenenfalls durch eine schnelle und wirksame Therapie gemildert werden und ist damit das eigentliche Ziel der medizinischen Therapie bei Schädelhirnverletzungen.

3. EPIDEMIOLOGIE

In Deutschland muss pro Jahr von 332 Patienten mit Schädelhirnverletzungen pro 100.000 Einwohner ausgegangen werden, davon sind 91 % als leicht, 4 % als mittel und 5 % als schwer einzustufen. Insgesamt ergibt das hochgerechnet ca. 248.000 Patienten mit SHT, wovon 2.750 Patienten versterben.. Die hochgerechneten gesamtgesellschaftlichen Kosten betragen für das SHT in Deutschland ca. 2,8 Milliarden €/Jahr [Rickels et al. 2006].

4. SYMPTOME

Subjektive Störungen nach einem SHT sind Kopfschmerzen, Benommenheitsgefühl, Übelkeit oder Schwindel, aber auch Doppelbilder und Schwerhörigkeit.

Objektive Verletzungszeichen des Kopfes sind Schwellung, Blutung, Riss- oder Platzwunden, Skalpierung, Deformitäten des Schädels, Austritt von Blut, Liquor oder Hirngewebe, Blutung aus Mund, Nase oder Ohr.

Hinweise auf eine Schädigung des Nervensystems sind Amnesie, Wachheitsstörungen, Orientierungsstörungen, Erbrechen, Lähmungen, Sprach- und/oder Koordinationsstörungen, Hirnnervenstörungen, Krampfanfälle, Streckkrämpfe, vegetative Störungen.

Eine Störung des Bewusstseins weist auf eine schwerwiegende Funktionsstörung des Gehirns hin. Hier ist zu unterscheiden zwischen einer

Bewusstseinstrübung: Reduzierte Wachheit, die Orientierung zu Person, Ort und Zeit ist eingeschränkt oder fehlt, die Augen können geöffnet werden

und einer

Bewusstlosigkeit (Koma): Fehlen geistiger Wahrnehmung der Umgebung und seiner selbst. Die klinischen Zeichen hierfür sind: nicht erweckbarer Zustand, Augen werden weder spontan noch auf Schmerzreiz geöffnet, Aufforderungen werden nicht befolgt, spontane Bewegungen sind möglich. In der Glasgow Coma Scale (s. Abschnitt 5 - Diagnostik) entspricht dies Werten unter 8.

Zeichen einer lebensbedrohlichen Verschlechterung beim bewusstseinsgestörten Patienten sind Pupillenerweiterung, gestörte Pupillenreaktion auf Licht, Hemiparese, Beuge- u. Strecksynergismen und Kreislaufstörungen.

[Brihaye et al. 1978, Frowein 1976, Gurdjian et al. 1979, Lorenz 1990, Teasdale and Jennett 1974, 1976]

Zur Klassifikation der Schwere des Schädelhirntraumas

Das Schädel-Hirn-Trauma ist insbesondere in der Akutphase eine dynamische Störung. Da sowohl eine rasche Verschlechterung als auch Verbesserung des klinischen Erscheinungsbildes auftreten kann, muss die anfängliche Abschätzung des Verletzungsgrades oft dem klinischen Verlauf angepasst werden.

International am häufigsten verwandt wird die Einteilung in die drei Schweregrade *leicht*, *mittelschwer* und *schwer*. Sie wird heute auf die in der Glasgow Coma Scale (s. Abschnitt 5 - Diagnostik) erfassten neurologischen Teilbefunde bzw. den daraus ermittelten Summenscore bezogen. Hinsichtlich des besten Zeitpunktes der GCS-Erhebung (nach Stabilisierung am Unfallort, nach Einlieferung ins Krankenhaus, nach 6 oder 12 Stunden, schlechtester Wert innerhalb 48 Stunden usw...) gibt es verschiedene Vorschläge, von denen sich bislang keiner durchsetzen konnte. Zusammen mit methodischen Schwächen bei der nicht immer gleich bedeutenden Summenbildung ist die Reliabilität und Validität dieser Klassifikation mit Vorbehalt zu sehen.

Die in Deutschland entwickelte Einteilung nach Tönnis und Loew in drei Schweregrade beruht auf der Dauer neurologischer Störungen und ist frühestens nach 3 Wochen, d. h. de facto nur retrospektiv anwendbar.

Der Schweregrad ist für die Versorgung des aktuellen Patienten aber von untergeordneter Bedeutung. **Die Behandlung richtet sich nach dem aktuellen klinisch-neurologischen Befund und dessen Verlauf**, der durch wiederholte (und vor allem in der Frühphase engmaschige) Untersuchungen erfasst werden muss

[Balestreri et al. 2004, Brain Trauma Foundation 2000 - Management and Prognosis of Severe Traumatic Brain Injury, Gabriel et al. 2002 - , Kraus et al. 1984 Maas et al 1997, Marion und Carlier 1994, Moskopp et al. 1995, Tönnis und Loew 1953].

Weitere Verletzungen beim Schädelhirntrauma

Bei jedem bewusstlosen Patienten ist nach Schädelhirntrauma grundsätzlich die Möglichkeit mehrfacher lebensbedrohlicher Verletzungen (bedeutungsgleich mit **Polytrauma**) zu unterstellen. Da der bewusstlose Patient weder zum Unfallhergang noch zu seinen Beschwerden und Schmerzen selbst Angaben machen kann, sind weitere Verletzungen durch sorgfältige Zusatzuntersuchungen auszuschließen. Insbesondere Verletzungen des Respirationstraktes mit konsekutiver Hypoxie und ein hämodynamisch relevanter Blutverlust, der auch in körpereigene Kompartimente (Bauch-, Thoraxtrauma, multiple Frakturen) erfolgen kann, verstärken die zerebrale Schädigung erheblich. Diese Situation sollte daher sofort erkannt werden und bedarf sofortiger Gegenmaßnahmen (s. unten).

Ca. 15 % der Patienten mit schwerem Schädelhirntrauma haben begleitende Verletzungen der Wirbelsäule bzw. des kraniozervikalen Überganges. Bis zum radiologischen Beweis des Gegenteils sollte daher bei bewusstlosen Patienten von einer instabilen Wirbelsäulenverletzung ausgegangen werden.

Durch die Gewalteinwirkung auf den Schädel kann es zur Verletzung der hirnversorgenden **Gefäße** kommen mit Dissektion, Ausbildung eines traumatischen Aneurysmas und insbesondere bei basalen Frakturen zur Ausbildung einer arteriovenösen Fistel (Carotis-cavernosus-Fistel).

5. MAßNAHMEN AM UNFALLORT – PRÄKLINISCHE VERSORGUNG

Sofortmaßnahmen

E1	**A**	**Bewusstlose Patienten (Anhaltsgröße GCS ≤ 8) sollen intubiert werden und für ausreichende (Be-) Atmung ist zu sorgen.**
E2	**B**	**Ein Absinken der arteriellen Sauerstoffsättigung unter 90 % sollte vermieden werden**
E3	**B**	**Beim Erwachsenen sollte versucht werden, den systolischen Blutdruck nicht unter 90 mmHg sinken zu lassen**

Nach Schädelhirntrauma sind Hypoxie und arterielle Hypotension in einem signifikanten Ausmaß mit einer schlechteren klinischen Erholung verbunden [Gabriel et al. 2002 – Assessment: Oxygenation and Blood Pressure]. Absolute Priorität der diagnostischen und therapeutischen Maßnahmen am Unfallort hat daher die Erkennung und nach Möglichkeit die sofortige Beseitigung aller Zustände, die mit einem Blutdruckabfall oder einer Abnahme der Sauerstoffsättigung im Blut einhergehen (ABC-Regel). Bei Hirnverletzten ist jederzeit damit zu rechnen, dass eine Verschlechterung der Atmung eintritt, so dass vorbeugende Maßnahmen zur Sicherstellung der Sauerstoffversorgung des Gehirns von oberster Dringlichkeit sind.

Bei bewusstlosen Patienten (Anhaltsgröße GCS ≤ 8) besteht die Indikation zur Intubation, und für ausreichende (Be-)Atmung ist zu sorgen ***(Empfehlung E1).*** Nachdem diese Empfehlung bislang auf einem Expertenkonsens beruhte, konnte in jüngster Zeit gezeigt werden, dass durch eine frühe Intubation bewußtloser Patienten das Behandlungsergebnis nach 6 Monaten verbessert werden konnte. Begleitende, atmungsrelevante Verletzungen - Pneumothorax, Hämatothorax - müssen erkannt und notfallmäßig behandelt werden.

Anzustreben sind eine Normoxie und Normocapnie. Ein Absinken der arteriellen Sauerstoffsättigung unter 90 % sollte vermieden werden .

Hierzu müssen Herz-Kreislauffunktionen durch Stillen offensichtlicher Blutungen, Überwachung von Blutdruck und Puls sowie Substitution von Flüssigkeitsverlusten sicher gestellt werden.

Anzustreben ist eine arterielle Normotonie. Beim Erwachsenen sollte versucht werden, den systolischen Blutdruck nicht unter 90 mmHg sinken zu lassen [Brain Trauma Foundation 2007 - Blood Pressure and Oxygenation, Gabriel et al. 2002 - Treatment: Fluid Resuscitation

[Bertrand et al 2010, The Brain trauma foundation 2007 Gabriel et al. 2002, Ghajar 2000].

Anamnese

E4	**A**	**Neben dem klinischen Befund gibt die Anamnese Hinweise auf eine potentielle intrakranielle Verletzung. Sie soll daher unbedingt erhoben werden**

Neben dem klinischen Befund gibt die Anamnese Hinweise auf eine potentielle intrakranielle Verletzung. Sie soll daher unbedingt erhoben werden. Angaben über die Art der Fahrzeugbeschädigung oder die Absturzhöhe liefern Informationen über die Gewalteinwirkung und das mögliche Ausmaß einer Verletzung und haben damit Bedeutung für das weitere Vorgehen (z. B. für die Indikation einer CT-Untersuchung - s. Abschnitt Akutversorgung im Krankenhaus). Gegebenenfalls liefert auch die Fremdanamnese (Befragung weiterer Unfallbeteiligter oder -zeugen) wichtige Hinweise, insbesondere der Hinweis auf einen initial, aktuell aber nicht mehr bewusstseinsklaren Patienten muss als Ausdruck einer sich verschlechternden intrakraniellen Verletzung gewertet werden. Wesentlich ist auch die zeitnahe Erhebung einer Medikamentenanamnese (z. B. Einnahme blutgerinnungshemmender Medikamente).

Neurologische Untersuchung

E5	**A**	Folgende Parameter zum neurologischen Befund Bewusstseinsklarheit, Bewusstseinstrübung oder Bewusstlosigkeit Pupillenfunktion und Motorische Funktionen seitendifferent an Armen und Beinen sollen erfasst und dokumentiert werden
E6	**B**	Kurzfristige Kontrollen des neurologischen Befundes zur Erkennung einer Verschlechterung sollten durchgeführt werden.
E7	**B**	Der neurologische Befund sollte standardisiert erhoben werden. International hat sich hierfür die GCS eingebürgert. Die Limitationen der Skala (Scheinverbesserungen, Befund bei Intubation, Analgosedierung u.a.) müssen berücksichtigt werden

Unverzichtbar sind die Erfassung und Dokumentation von

- Bewusstseinsklarheit, Bewusstseinstrübung oder Bewusstlosigkeit
- Pupillenfunktion
- Motorische Funktionen der Extremitäten mit seitengetrennter Unterscheidung an Arm und Bein, ob keine, eine unvollständige oder eine vollständige Lähmung vorliegt. Sofern keine Willkürbewegungen möglich sind, muss die Reaktion auf Schmerzreiz erfasst werden. Hierbei sollte auf das Vorliegen von Beuge- oder Strecksynergismen geachtet werden.

  Liegt keine Bewusstlosigkeit vor, sind zusätzlich Orientierung, Hirnnervenfunktion, Koordination und Sprachfunktion zu erfassen.

  Diese neurologischen Befunde, mit Uhrzeit dokumentiert (s. auch DIVI-Protokoll), sind entscheidend für den Ablauf der weiteren Behandlung. Kurzfristige Kontrollen des neurologischen Befundes zur Erkennung einer Verschlechterung sind anzuraten.

In der Beurteilung schädelhirntraumatisierter Patienten hat sich die Glasgow-Coma-Scale international als Einschätzung der momentan festzustellenden Schwere einer Hirnfunktionsstörung eingebürgert. Mit ihr können die Aspekte *Augenöffnen*, *verbale Kommunikation* und *motorische Reaktion* standardisiert bewertet werden. Fehlbeur-

teilungen sind bei bewussstlosen Patienten durch die Besonderheit des GCS möglich, dass die prognostisch ungünstigen Zeichen der Bewusstlosigkeit im GCS allein anhand der **besten** motorischen Funktionen differenziert werden. Damit werden die wichtigsten akuten klinischen Zeichen der unmittelbar lebensbedrohlichen Einklemmung des Bewusstlosen, die Störung der Pupillenfunktion und die Streck- und Beugesynergismen, im GCS nicht bzw. nicht hinreichend berücksichtigt. Die Skalenbewertung ist bei bewusstlosen Patienten damit im Einzelfall irreführend und einer detaillierten neurologischen Funktionserhebung und –diagnostik sicher unterlegen.

[Balestreri et al. 2004 The Brain Trauma Foundation 2000, Gabriel et al. 2002 Karimi und Burchardi 2004, Moskopp et al. 1995].

Schädelhirntrauma bei Bewusstseinsstörung aus anderer Ursache

In einzelnen Fällen führt eine akut einsetzende Bewusstseinsstörung zu einem Unfallgeschehen mit Schädelhirntrauma. Eine während der Versorgung am Unfallort einfach zu erkennende und sofort zu therapierende Ursache ist die Hypoglykämie. Neben endokrinologischen und metabolischen Ursachen ist auch an kardiovaskuläre und zerebrovaskuläre Erkrankungen (Herzinfarkt, Lungenembolie, Schlaganfall, Subarachnoidalblutung) sowie andere Gründe wie Intoxikation und Hypothermie zu denken [Gabriel et al. 2002 - Brain-Targeted Therapy].

Indikationen für eine Einweisung in ein Krankenhaus

E8	**A**	**Bei Vorliegen folgender Symptome soll unbedingt eine stationäre Einweisung zur weiteren diagnostischen Abklärung und ggf. Beobachtung des Patienten erfolgen:** **Koma** **Bewusstseinstrübung** **Amnesie** **andere neurologische Störungen** **Krampfanfall** **Klinische Zeichen oder röntgenologischer Nachweis einer Schädelfraktur** **Verdacht auf Impressionsfraktur und/oder penetrierende Verletzungen** **Verdacht auf nasale oder otogene Liquorfistel**
E9	**B**	**Bei folgenden Symptomen im Zusammenhang mit einer Gewalteinwirkung auf den Schädel sollte die Einweisung in ein Krankenhaus erfolgen:** **Erbrechen, wenn ein enger zeitlicher Zusammenhang zur Gewalteinwirkung besteht.** **Bei Hinweisen auf eine Gerinnungsstörung (Fremdanamnese, "Pass zur Antikoagulanzienbehandlung", nicht sistierende Blutung aus oberflächlichen Verletzungen usw.)** **Im Zweifel**
E10	**A**	**Die Wahl der Klinik soll sich nach ihrer bestmöglichen Erreichbarkeit hinsichtlich Entfernung bzw. Transportzeit und der Ausstattung richten.**

E11	**A**	**Im Falle eines Schädelhirntraumas mit anhaltender Bewusstlosigkeit (GCS < 8), einer zunehmenden Eintrübung (Verschlechterung einzelner GCS-Werte), Pupillenstörung, Lähmung oder Anfällen soll die Klinik über die Möglichkeit einer neurochirurgischen Versorgung intrakranieller Verletzungen verfügen**

Bei Vorliegen folgender Symptome ist eine stationäre Einweisung zur weiteren diagnostischen Abklärung und ggf. Beobachtung des Patienten **unabdingbar**:

- Koma
- Bewusstseinstrübung
- Amnesie
- andere neurologische Störungen
- Krampfanfall
- Klinische Zeichen oder röntgenologischer Nachweis einer Schädelfraktur
- Verdacht auf Impressionsfraktur und/oder penetrierende Verletzungen
- Verdacht auf nasale oder otogene Liquorfistel

Bei folgenden Symptomen im Zusammenhang mit einer Gewalteinwirkung auf den Schädel ist die Einweisung in ein Krankenhaus **ratsam**:

- Erbrechen, wenn ein enger zeitlicher Zusammenhang zur Gewalteinwirkung besteht.
- Bei Hinweisen auf eine Gerinnungsstörung (Fremdanamnese, "Pass zur Antikoagulanzienbehandlung", nicht sistierende Blutung aus oberflächlichen Verletzungen usw.)
- Im Zweifel

Die Wahl der Klinik richtet sich nach ihrer bestmöglichen Erreichbarkeit hinsichtlich Entfernung bzw. Transportzeit und der Ausstattung. Im Falle eines Schädelhirntraumas mit anhaltender Bewusstlosigkeit (GCS < 8), einer zunehmenden Eintrübung (Verschlechterung einzelner GCS-Werte), Pupillenstörung, Lähmung oder Anfällen sollte die Klinik auf jeden Fall über die Möglichkeit einer neurochirurgischen Versorgung intrakranieller Verletzungen verfügen [Gabriel et al. 2002].

Transport

E12	**0**	**Zur Frage der Analgosedierung und Relaxierung für den Transport kann keine eindeutige Empfehlung ausgesprochen werden**

Zur Frage der Analgosedierung und Relaxierung für den Transport kann keine eindeutige Empfehlung ausgesprochen werden, da Studien fehlen, die eine positive Wirkung belegen. Die kardiopulmonale Versorgung ist sicherlich mit diesen Maßnahmen einfacher zu gewährleisten, sodass dies in das Ermessen des versorgenden Notarztes gestellt werden muss. Der Nachteil dieser Maßnahmen ist eine mehr oder weniger starke Einschränkung der neurologischen Beurteilbarkeit.

Bei perforierenden Verletzungen sollte der perforierende Gegenstand belassen werden, evtl. muss er abgetrennt werden. Bewusstlose Patienten sollten bis zum Beweis des Gegenteils in der radiologischen Diagnostik so behandelt werden, als ob sie eine instabile Wirbelsäulenfraktur haben (Immobilisierung mit fester Halskrawatte - "stiff neck", Lagerung en bloc, Vakuummatratze)

[Brain Trauma Foundation 2000 – Initial Management].

Hirnprotektive Therapie

E13	**A**	**Auf die Gabe von Glukokortikoiden zur Behandlung des SHT soll aufgrund einer signifikant erhöhten 14Tage-Letalität, verzichtet werden**
E14	**0**	**Bei Verdacht auf transtentorielle Herniation und den Zeichen des Mittelhirnsyndroms (Pupillenerweiterung, Strecksynergismen, Streckreaktion auf Schmerzreiz, progrediente Bewusstseinstrübung) kann durch die Gabe von Mannitol oder hypertoner Kochsalzlösung eine Senkung des intrakraniellen Druckes versucht werden**
E15	**0**	**In den Fällen mit Verdacht auf transtentorielle Herniation und den Zeichen des Mittelhirnsyndroms (Pupillenerweiterung, Strecksynergismen, Streckreaktion auf Schmerzreiz, progrediente Bewusstseinstrübung) kann die Hyperventilation als Behandlungsoption in der Frühphase nach Trauma eingesetzt werden.**

Auf die lange Zeit umstrittene Gabe von **Glukokortikoiden** sollte nach neuesten Erkenntnissen aufgrund einer signifikant erhöhten 14Tage-Letalität verzichtet werden. Dieses bezieht sich auf das isolierte SHT aller Schweregrade. Liegen weitere Umstände vor, die einen Einsatz von Glukokortikoiden indizieren (z.B. schwerwiegende Atemwegsschwellung), muß eine individuelle Güterabwägung getroffen werden.

Die Gabe von **Mannitol und hypersomolaren Lösungen** können für einen kurzen Zeitraum (bis 1 Std.) den intrakraniellen Druck (intracranial pressure - ICP) senken. Bei Verdacht auf transtentorielle Herniation ist die Gabe auch ohne Messung des ICP gerechtfertigt. Für den Nutzen einer darüber hinausgehenden Anwendung in der Prähospitalphase gibt es jedoch keine Evidenz.

In den Fällen mit Verdacht auf transtentorielle Herniation und den Zeichen des Mittelhirnsyndroms (Pupillenerweiterung, Strecksynergismen, Streckreaktion auf Schmerzreiz, progrediente Bewusstseinstrübung) kann die **Hyperventilation** als Behandlungsoption in der Frühphase nach Trauma eingesetzt werden . Richtwerte sind 20 Atemzüge/min bei Erwachsenen.

Die Gabe von Barbituraten, die in früheren Leitlinien bei anderweitig nicht beherrschbaren Hirndruckkrisen empfohlen wurde , ist nicht ausreichend belegt . Auf die negativ inotrope Wirkung und den möglichen Blutdruckabfall bei Barbituratgabe muss geachtet werden.

Eine **antikonvulsive Therapie** verhindert das Auftreten epileptischer Anfälle in der ersten Woche nach Trauma. Spätepilepsien werden hierdurch jedoch nicht verhindert. Das Auftreten von Anfällen in der Frühphase führt nicht zu einem schlechteren klinischen Ergebnis. [Schierhout and Roberts, 2012]

Die Ergebnisse in klinischen Studien haben bisher nicht den Nutzen weiterer medikamentöser Therapieregime belegen können, denen aufgrund experimenteller Untersuchungen eine hirnprotektive Wirkung zugeschrieben wird. Derzeit kann keine Empfehlung für die Gabe von 21-Aminosteroiden, Kalziumantagonisten, Glutamat-Rezeptor-Antagonisten, Tris-Puffer usw. gegeben werden

[Alderson and Roberts 2005, Brain Trauma Foundation 2007 - Antiseizure Prophylaxis, Brain Trauma Foundation 2007 - Hyperosmolar Therapy, Brain Trauma Foundation 2000 - Hyperventilation, Brain Trauma Foundation 2000 - Use of barbiturates in the control of intracranial hypertension,Bourdeaux et al. 2011, Bulger et al. 2010, Cottenceau et al. 2011, Gabriel et al. 2002 - Brain-targeted therapy, Langham et al.

2004, Roberts et al. 2003 Roberts 2004 a, Roberts 2004 b, Roberts et al. 2009 Roberts und Sydenham 2012 Schierhout and Roberts 2012, Wakai et al. 2013 Willis et al. 2004].

Dokumentation

E16	**A**	**Für die weitere Versorgung des schädelhirnverletzten Patienten sind Angaben zum Unfallmechanismus, der initiale Befund und der weitere Verlauf von großer Bedeutung. Sobald die Versorgung des Patienten es erlaubt, sollten die Angaben schriftlich dokumentiert werden**

Für die weitere Versorgung des schädelhirnverletzten Patienten sind Angaben zum Unfallmechanismus, der initiale Befund und der weitere Verlauf von großer Bedeutung. Sobald die Versorgung des Patienten es erlaubt, sollten die Angaben schriftlich dokumentiert werden. Hierfür bietet sich das DIVI-Notarzteinsatzprotokoll an.

6. AKUTVERSORGUNG IM KRANKENHAUS

Aufgrund der im Kapitel 4 erwähnten Möglichkeit einer bislang nicht erkannten Mehrfachverletzung ist für bewusstlose Patienten eine interdisziplinäre Versorgung bei der Einlieferung ins Krankenhaus dringend anzuraten (z. B. in einem interdisziplinär betriebenen Schockraum).

Nach Überprüfung des klinischen Befundes, ggf. der Sicherstellung der Vitalfunktionen ist in der Regel eine bildgebende Diagnostik erforderlich. Unmittelbar lebensbedrohliche Verletzungsfolgen, Blutungen in die großen Körperhöhlen (Schädel, Thorax, Abdomen) müssen vorrangig vor nicht lebensbedrohlichen Verletzungsfolgen diagnostiziert werden. Bei bewusstlosen Verletzten müssen grundsätzlich sowohl eine akut lebensbedrohliche intrakranielle Blutung als auch lebensbedrohliche Mehrfachverletzungen unterstellt werden. Hinweise ergeben sich aus der Vorgeschichte und dem ersten Untersuchungsbefund.

Bildgebende Diagnostik

E17	**A**	**Die kraniale CT gilt als Goldstandard und soll bei schädelhirnverletzten Patienten durchgeführt werden, wenn folgende Befunde vorliegen bzw. bekannt sind (absolute Indikation):** **Koma** **Bewusstseinstrübung** **Amnesie** **andere neurologische Störungen** **mehrfaches Erbrechen, wenn ein enger zeitlicher Zusammenhang zur Gewalteinwirkung besteht.** **Krampfanfall** **Zeichen einer Schädelfraktur** **Verdacht auf Impressionsfraktur und/oder penetrierende Verletzungen** **Verdacht auf Liquorfistel** **Hinweise auf eine Gerinnungsstörung (Fremdanamnese, "Pass zur Antikoagulanzienbehandlung", nicht sistierende Blutung aus oberflächlichen Verletzungen usw.)**
E18	**B**	**Eine kraniale CT sollte in Zweifelsfällen durchgeführt werden (fakultative Indikation), z. B. bei:** **unklaren Angaben über die Unfallanamnese** **starken Kopfschmerzen** **Intoxikation mit Alkohol oder Drogen** **Hinweisen auf ein Hochenergietrauma**
E19	**0**	**Die Magnetresonanztomographie kann aufgrund ihrer höheren Sensitivität für umschriebene Gewebsläsionen nach der Akutversorgung zur Abklärung von Patienten mit neurologischen Störungen ohne pathologischen CT Befund eingesetzt werden**

Da die sofortige Entfernung einer intrakraniellen Blutung lebensrettend sein kann, ist bei stabiler Atem- und Kreislauffunktion eine Verzögerung des sofort notwendigen Schädel-CT (s. unten) nicht gerechtfertigt. Auch für den am Unfallort ansprechbaren, für Intubation und Transport sedierten Verletzten gilt diese Forderung, weil die Unterscheidung einer sich entwickelnden intrakraniellen Blutung von einer medikamentösen Ursache der Bewusstlosigkeit nur mittels CT möglich ist. Die schnellste und in Hinblick auf die weitere Behandlung aussagekräftigste bildgebende Diagnostik bei Mehrfachverletzung stellt ein Spiral-CT des Schädels, Thorax und Abdomens dar. Nach Ausschluss bzw. Behandlung der akut lebensbedrohlichen Verletzungsfolgen sind knöcherne und je nach Umständen andere Verletzungen auszuschließen.

Bei fakultativer Indikation ist alternativ zum CT eine engmaschige neurologische Überwachung möglich. Es gibt Hinweise darauf, dass bei einem S 100 Wert unter 0,14 µg/l auf ein Schädel-CT verzichtet werden kann (Biberthaler et al. 2004).

Steht ein CT-Gerät nicht zur Verfügung, so sollte der Nachweis einer Fraktur in den Röntgenaufnahmen des Schädels eine Verlegung in ein Krankenhaus mit entspre-

chender Ausstattung veranlassen. Der fehlende Nachweis einer knöchernen Verletzung schließt aber eine intrakranielle Blutung keineswegs aus.

Im Falle einer neurologischen Verschlechterung ist die Durchführung einer Kontroll-CT selbstverständlich. Auch bei fehlender Erholung oder bewusstlosen Patienten ist ein Verlaufs-CT nach 4 - 8 Stunden ratsam (Advanced Trauma Life Support (ATLS) 2004, Pandor et al. 2012, Mendelow et al. 1983).

Aufgrund des hohen apparativen Aufwandes bei schwer verletzten Patienten eignet sich die MRT nicht als primäre bildgebende Untersuchung in der Akutsituation. Im Vergleich zur CT hat sie jedoch eine höhere Sensitivität für umschriebene Gewebsläsionen. Sie wird daher vor allem bei Patienten mit neurologischen Störungen ohne pathologischen CT Befund empfohlen (Firsching et al. 2001, Vos et al. 2006).

Indikation für den stationären Verbleib im Krankenhaus

E20	**A**	**Eine stationäre Aufnahme, ggf. operative Versorgung und Überwachung des Patienten, soll erfolgen im Falle von:** **operativ zu versorgenden Verletzungsfolgen** **Bewusstseinsstörung, Bewusstlosigkeit** **neurologischen Störungen** **Schädelfraktur** **Liquoraustritt, offener Schädelhirnverletzung** **im CT erkennbaren Verletzungsfolgen**
E21	**B**	**Darüber hinaus sollte die stationäre Aufnahme im Zweifelsfall (z.B. starke Kopfschmerzen, Übelkeit, Intoxikation mit Drogen oder Alkohol) erfolgen**

7. THERAPIE

Ziel der Therapie nach einem SHT ist es, das Ausmaß der eingangs erwähnten sekundären Hirnschädigung zu begrenzen und den funktionsgeschädigten, aber nicht zerstörten Zellen des Gehirns optimale Bedingungen für die funktionelle Regeneration zu geben. Operationspflichtige Verletzungsfolgen müssen rechtzeitig behandelt werden. Die Therapie beginnt am Unfallort (s. Abschnitt 5 - Maßnahmen am Unfallort) und setzt sich im Krankenhaus fort.

Notfallmäßige operative Versorgung

E22	**A**	**Raumfordernde, intrakranielle Verletzungen sollen operativ entlastet werden**

Die Indikation für eine operative Entlastung einer traumatischen intrakraniellen Raumforderung ist nie durch prospektiv randomisierte und kontrollierte Studien überprüft worden. Es gibt mehrere retrospektive Analysen aus denen der Nutzen einer operativen Dekompression ebenfalls ableitbar ist. Aufgrund der jahrzehntelangen, übereinstimmenden Erfahrung kann die Notwendigkeit des operativen Vorgehens als eine Grundannahme guter klinischer Praxis angesehen werden, die nicht in Frage gestellt wird

[s. Übersicht in Bullock et al. 2006 a - g, Fernandez et al. 1997, Firsching et al. 1997], .

Raumfordernde, intrakranielle Verletzungen stellen eine absolut dringliche Operationsindikation dar. Dies gilt sowohl für traumatische intrakranielle Blutungen (Epiduralhämatom, Subduralhämatom, Intrazerebralhämatom/Kontusion) als auch für raumfordernde Impressionsfrakturen. Die Definition der Raumforderung ergibt sich dabei durch die Verlagerung zerebraler Strukturen, insbesondere des normalerweise in der Mittellinie gelegenen 3. Ventrikels. Neben dem Befund in der Computertomographie (Dicke, Volumen und Lokalisation des Hämatoms, Ausmaß der Mittellinienverlagerung) ist der klinische Befund entscheidend für die Indikationsstellung und die Schnelligkeit, mit der die operative Versorgung zu erfolgen hat. Bei Zeichen einer transtentoriellen Herniation können Minuten über das klinische Ergebnis entscheiden.

Operationen mit aufgeschobener Dringlichkeit

E23	**B**	**Offene oder geschlossene Impressionsfrakturen ohne Verlagerung der Mittellinienstrukturen, penetrierende Verletzungen und basale Frakturen mit Liquorrhoe, für die eine operative Indikation besteht, sollten ggf. mit aufgeschobener Dringlichkeit versorgt werden**
E24	**B**	**Nicht vital erforderliche Operationen von Begleitverletzungen sollten im Rahmen der Primärversorgung nur durchgeführt werden, soweit sie für die Herstellung einer adäquaten Intensivtherapie erforderlich sind**

Offene oder geschlossene Impressionsfrakturen ohne Verlagerung der Mittellinienstrukturen, penetrierende Verletzungen und basale Frakturen mit Liquorrhoe stellen Operationen mit aufgeschobener Dringlichkeit dar. Ihre Durchführung bedarf neurochirurgischer Kompetenz. Der Zeitpunkt des operativen Eingriffes hängt dabei von vielen Faktoren ab und muss individuell vom Neurochirurgen festgelegt werden.

Nicht vital erforderliche Operationen von Begleitverletzungen sollten im Rahmen der Primärversorgung nur durchgeführt werden, soweit sie für die Herstellung einer adäquaten Intensivtherapie erforderlich sind. Dabei dürfen keine größeren Blutverluste oder Volumenverschiebungen entstehen. Die Methodenwahl richtet sich nach den Prinzipien der "damage control surgery" . Im weiteren Verlauf sollten Eingriffe, die nicht aus den genannten Gründen erforderlich sind, bei anhaltender Bewusstlosigkeit zurückgestellt werden, bis der Zustand des Patienten hinreichend stabil erscheint.

[Fernandez et al. 1997, Maas et al. 1997, Rotondo et al. 1993].

Entlastungskraniektomie

E25	**0**	**Aufgrund der effektiven Senkung des erhöhten intrakraniellen Druckes kann die operative Dekompression durch Kraniektomie und Duraerweiterungsplastik bei erhöhtem Hirndruck erfolgen. Eine Beeinflussung des klinischen Ergebnisses ist bislang nicht durch hochwertige Studien belegt.**

Die wirksamste Möglichkeit, den erhöhten intrakraniellen Druck zu senken, ist die operative Dekompression durch Kraniektomie und Duraerweiterungsplastik. Die Notwendigkeit ergibt sich meist bei Entwicklung eines ausgeprägten (sekundären) Hirnödems und daher häufiger mit einer mehrtägigen Latenz, sie kann in Einzelfällen auch unmittelbar nach Unfall bei Schwellungsreaktionen hilfreich sein. Die Methode

ist nach einzelnen Studien mit unterschiedlichem Behandlungserfolg zurzeit Gegenstand wissenschaftlicher Untersuchungen und kann daher noch nicht abschließend bewertet werden.

[Cooper et al. 2011, Qui et al. 2009, Sahuquillo et al 2006].

Nicht operative Behandlung intrakranieller Blutungen

E26	**0**	**In Einzelfällen kann bei nicht raumfordernden Blutungen und stabilem neurologischem Befund ein nicht operatives Vorgehen gerechtfertigt sein**

In Einzelfällen ist bei nicht raumfordernden Blutungen und stabilem neurologischem Befund ein nicht operatives Vorgehen gerechtfertigt. Diese Patienten müssen aber einer engmaschigen klinischen und computertomographischen Verlaufsbeobachtung unterzogen werden. Im Falle einer klinischen Verschlechterung oder Zunahme der Raumforderung muss eine sofortige operative Entlastung durchführbar sein

[Bullock et al. 2006 c – f].

Messung des intrakraniellen Druckes

E27	**B**	**Die Messung des intrakraniellen Druckes sollte aus pathophysiologischen Überlegungen heraus erfolgen, zumal bei SHT-Patienten die klinische Überwachung vieler zerebraler Funktionen nur eingeschränkt möglich ist.**
E28	**B**	**Im Falle einer intrakraniellen Druckmessung sollten Maßnahmen ergriffen werden, die den CPP nicht unter 50 mmHg sinken lassen.**
E29	**B**	**Im Falle einer intrakraniellen Druckmessung sollte der CPP nicht durch eine aggressive Therapie über 70 mmHg angehoben werden**
E30	**B**	**Zur kontinuierlichen Bestimmung des CPP ist eine invasive ICP-Messung erforderlich. Solange die Ventrikel nicht vollständig ausgepresst sind, sollte das ICP-Monitoring über eine Ventrikeldrainage erfolgen. Sie bietet die Möglichkeit, durch Ablassen von Liquor einen erhöhten ICP zu senken.**

Die Messung des intrakraniellen Druckes hat in den letzten Jahrzehnten international ihren Einzug in die Akutversorgung bewusstloser schädelhirnverletzter Patienten gefunden und wurde mittlerweile in mehreren internationalen Leitlinien implementiert. Aus pathophysiologischen Überlegungen heraus erscheint sie sinnvoll, da die klinische Überwachung vieler zerebraler Funktionen nur eingeschränkt möglich ist. Sie kann bei sedierten Patienten als Instrument der Überwachung auf eine drohende Mittelhirneinklemmung durch progrediente Hirnschwellung oder raumfordernde intrakranielle Hämatome hinweisen und erlaubt so, frühzeitig Gegenmaßnahmen zu ergreifen. Auch wenn es derzeit keine prospektive randomisiert-kontrollierte Studie gibt, die das klinische Ergebnis in Relation zur Durchführung eines ICP-Monitorings setzt , weisen sowohl mehrere Kohortenstudien der letzten Jahre als auch die klinische Praxis auf ihren Wert für die neurochirurgische Intensivmedizin hin . Die Einführung von Leitlinien, die unter anderem ein solches ICP-Monitoring vorsehen, führte darüber hinaus zu einer Zunahme günstiger Verläufe bei SHT-Patienten. Die intrakrani-

elle Druckmessung wird von Neurochirurgen bei bewusstlosen Patienten unter Berücksichtigung des klinischen Verlaufes und der bildmorphologischen Befunde nach SHT zur Überwachung und Therapiesteuerung eingesetzt. Der praktische Nutzen der invasiv gemessenen ICP Werte wird kontrovers diskutiert, denn der ICP Wert, ab dem eine Behandlung erforderlich wäre, ist wissenschaftlich nicht belegt. Ebenso ist der Nutzen einer medikamentösen Senkung eines erhöhten ICP umstritten. Wenngleich die Risiken einer invasiven Hirndruckmessung insgesamt als niedrig eingeschätzt werden, muss das Risiko einer Komplikation der aus pathophysiologischen Gründen für sinnvoll erachteten invasiven Hirndruckmessung gegen den möglichen Nutzen abgewogen werden.

[Adelson et al. 2003/6,7,8, Brain Trauma foundation 2007 - Indications for Intracranial Pressure Monitoring, Balestreri et al. 2006, Blaha et al. 2003, Bullock et al. 1996 ,Chesnut et al. 2012, Fahkry et al 2004, Firsching et al. 2010, Forsyth et al. 2004b und 2010,Hiler et al. 2006, Lane et al. 2000, Maas et al 1997 Mauritz et al. 2007 Palmer et al 2001,Plötz et al. 2007 Shafi et al. 2008]

Voraussetzung einer ausreichenden Hirndurchblutung ist ein adäquater zerebraler Perfusionsdruck (cerebral perfusion pressure - CPP), der sich vereinfacht aus der Differenz des mittleren arteriellen Blutdruckes und des mittleren ICP errechnen lässt. Die Frage, ob bei erhöhtem ICP mehr die Senkung des ICP oder die Aufrechterhaltung des CPP im Vordergrund der Therapie stehen sollte, wird in der Literatur unterschiedlich beantwortet. Die derzeit vorliegende Evidenz spricht dafür, dass

- der CPP einerseits nicht unter 50 mmHg sinken sollte .
- der CPP andererseits nicht durch eine aggressive Therapie über 70 mmHg angehoben werden sollte.

Zur kontinuierlichen Bestimmung des CPP ist eine invasive ICP-Messung erforderlich. Solange die Ventrikel nicht vollständig ausgepresst sind, bietet das ICP-Monitoring über eine Ventrikeldrainage die Möglichkeit, durch Ablassen von Liquor einen erhöhten ICP zu senken.

Eine Bestimmung des individuell optimalen CPP setzt eine gleichzeitige Kenntnis von Hirndurchblutung, Sauerstoffversorgung und -bedarf und/oder Hirnstoffwechsel voraus. Regionale Messungen (mittels Parenchymsensoren, transkranieller Doppleruntersuchungen oder perfusionsgewichteter Bildgebung) zur Abschätzung dieses Wertes sind derzeitig Gegenstand wissenschaftlicher Untersuchungen

[Brain trauma foundation 2007 - Cerebral Perfusion Thresholds , Jaeger et al. 2006, Steiner et al. 2002]

Nicht operative Therapie

E31	**0**	**Osmodiuretika, z. B. Mannitol oder hypertone Kochsalzlösung können zur kurzzeitigen Senkung des ICP eingesetzt werden.**
E32	**0**	**Die Hyperventilation kann bei erhöhtem Hirndruck und akuter Gefahr einer transtentoriellen Herniation für einen kurzen Zeitraum hilfreich sein**
E33	**0**	**Die Oberkörperhochlagerung auf 30° kann zur Senkung extrem hoher ICP-Werte eingesetzt werden.**
E34	**0**	**Die (Analgo-)Sedierung ist eine Option, Unruhezustände zu vermeiden und eine Beatmung zu ermöglichen**

E35	**0**	**Die Gabe von Barbituraten kann bei anderweitig nicht beherrschbaren Krisen intrakranieller Hypertension erwogen werden**
E36	**0**	**Die hyperbare Sauerstofftherapie kann optional angewandt werden**
E37	**0**	**Die Hypothermie ist eine Behandlungsoption beim SHT**
E38	**0**	**Bei frontobasalen Frakturen mit Liquorrhoe kann eine Antibiotikagabe erwogen werden**
E39	**A**	**Auf die Gabe von Glukokortikoiden zur Behandlung des SHT soll aufgrund einer signifikant erhöhten 14Tage-Letalität, verzichtet werden**
E40	**0**	**Zur Vermeidung eines Anfalls in der ersten Woche kann eine antikonvulsive Therapie erfolgen**
E41	**B**	**Eine über ein bis zwei Wochen hinausgehende Antikonvulsivagabe sollte nur in Ausnahmefällen (z.B. vorbestehende Epilepsie, persistierende Anfälle) durchgeführt werden**
E42	**A**	**Die Thromboseprophylaxe mittels physikalischer Maßnahmen soll angewandt werden sofern keine Kontraindikationen vorliegen.**
E43	**0**	**Die Gabe von Heparin bzw. Heparinderivaten ist eine Option zur Vermeidung thromboembolischer Komplikationen. Die Anwendung ist umstritten .**
E44	**A**	**Mydriatica sollen bei bewusstlosen Patienten nach SHT grundsätzlich nicht angewandt werden, da nach ihrer Anwendung die Entwicklung einer Anisokorie mit Pupillenstarre als Frühzeichen einer intrakraniellen Einklemmung nicht mehr erfasst werden kann**

Bei schädelhirnverletzten Patienten ist eine Substitution ausgefallener Funktionen (Atmung, Nahrungsaufnahme erforderlich. Wesentliches Ziel zum gegenwärtigen Zeitpunkt der wissenschaftlichen Erkenntnis ist es, eine Homöostase (Normoxie, Normotonie, Vermeiden einer Hyperthermie,...) zu erreichen und drohende (z. B. infektiöse) Komplikationen abzuwenden. Sepsis, Pneumonie und Blutgerinnungsstörungen sind unabhängige Prädiktoren eines schlechten klinischen Ergebnisses []. Die hierzu bereits am Unfallort begonnenen Maßnahmen (s. Kapitel 5) werden im Krankenhaus, häufig im Rahmen einer intensivmedizinischen Behandlung, fortgesetzt.

Auch wenn es in der Literatur keine Evidenz für den Nutzen gibt (s. den obigen Abschnitt über die Messung des intrakraniellen Drucks), so stellt doch die Aufrechterhaltung eines adäquaten CPP aus pathophysiologischen Überlegungen heraus ein wichtiges Element dieser Homöostase dar. Dies beinhaltet die Vermeidung von Blutdruckabfällen, die gegebenenfalls den Einsatz von **Katecholaminen** erfordern. Zur Senkung eines erhöhten ICP andererseits stehen mehrere Möglichkeiten zur Verfügung:

Osmodiuretika, z. B. Mannitol oder hyperosmolare Lösungen bewirken eine kurzzeitige Senkung des ICP-. Auf die Serum-Osmolarität und die Nierenfunktion muss geachtet werden. Für die Gabe von Albumin findet sich keine Empfehlung.

Die **Hyperventilation** kann bei erhöhtem Hirndruck und akuter Gefahr einer transtentoriellen Herniation für einen kurzen Zeitraum hilfreich sein. Sie bewirkt über eine Vasokonstriktion eine Verminderung des intrakraniellen Blutvolumens und damit eine meist vorübergehende ICP-Senkung. Eine prolongierte Hyperventilation kann aber zu einer schlechteren Gewebsperfusion und damit zu nachteiligen Ergebnissen führen.. Sie sollte daher nur in begründeten Ausnahmefällen angewandt werden.

Die Oberkörperhochlagerung auf 30° wird häufig empfohlen, obwohl hierdurch der CPP nicht beeinflusst wird. Extrem hohe ICP-Werte werden jedoch reduziert.

Ziel der (**Analgo-)Sedierung ist es,** Unruhezustände zu vermeiden und eine hinreichende Beatmung zu ermöglichen.

Für die hirnprotektive Wirkung **hypertoner Kochsalzlösungen** gibt es bislang noch keine ausreichende Datenlage, die eine Empfehlung ermöglicht.

Der Nutzen der Gabe von **Barbituraten**, die in früheren Leitlinien bei anderweitig nicht beherrschbaren Hirndruckkrisen empfohlen wurde, ist nicht ausreichend belegt . Auf die negativ inotrope Wirkung, den möglichen Blutdruckabfall und die Beeinträchtigung der neurologischen Beurteilbarkeit bei Barbituratgabe muss geachtet werden.

Weitere beim SHT angewandte Therapiekonzepte sind:

Die **hyperbare Sauerstofftherapie**, deren Nutzen jedoch nicht belegt ist.

Der therapeutische Wert der **Hypothermie ist nicht geklärt.**

Der Wert **hemostatischer Medikamente** ist ungewiss. Die Gabe von Tranexamsäure ist als Option zu betrachten.

Die Notwendigkeit einer **antibiotischen Prophylaxe bei frontobasalen Frakturen mit Liquorrhoe** ist kontrovers diskutiert worden. Eine Evidenz für die Gabe von Antibiotika liegt jedoch nicht vor.

Auf die lange Zeit umstrittene Gabe von **Glukokortikoiden** sollte nach neuesten Erkenntnissen aufgrund einer signifikant erhöhten 14Tage-Letalität verzichtet werden.

Eine **antikonvulsive Therapie** verhindert das Auftreten epileptischer Anfälle in der ersten Woche nach Trauma. Das Auftreten eines Anfalls in der Frühphase führt jedoch nicht zu einem schlechteren klinischen Ergebnis.

Eine über ein bis zwei Wochen hinausgehende Antikonvulsivagabe ist nicht mit einer Reduktion spättraumatischer Anfälle verbunden.

Die Datenlage in der wissenschaftlichen Literatur hat bisher nicht den Nutzen weiterer, als spezifisch **hirnprotektiv** angesehener **Therapieregime** belegen können. Derzeit kann keine Empfehlung für die Gabe von 21-Aminosteroiden, Kalziumantagonisten, Glutamat-Rezeptor-Antagonisten, Tris-Puffer usw. gegeben werden.

Die Thromboseprophylaxe mittels physikalischer Maßnahmen (z. B. Kompressionsstrümpfe) ist eine unumstrittene Maßnahme zur Vermeidung von Sekundärkomplikationen. Bei der Gabe von Heparin bzw. Heparinderivaten muß der Nutzen gegenüber der Gefahr einer Größenzunahme intrakranieller Blutungen abgewogen werden, da es bei Hirnverletzungen keine Zulassung für diese Präparate gibt und daher die Anwendung außerhalb des Zulassungsbereiches zustimmungspflichtig durch den Patienten oder seinen gesetzlichen Vertreter ist. Die Gabe von Tranexamsäure ist als Option zu betrachten.

Mydriatica sind bei bewusstlosen Patienten nach SHT grundsätzlich kontraindiziert, da nach ihrer Anwendung die Entwicklung einer Anisokorie mit Pupillenstarre als Frühzeichen einer intrakraniellen Einklemmung nicht mehr erfasst werden kann.

[Alderson et al. 2004, Alderson and Roberts 2005, Bennett and Heard 2004, Brain Trauma Foundation 2007 - Hyperosmolar Therapy Brain Trauma Foundation 2007 – Hyperventilation, Brain Trauma Foundation 2000 - Use of barbiturates in the control of intracranial hypertension, Bourdeaux et al. 2011, Brain Trauma Foundation 2007 - Nutrition, Brain Trauma Foundation 2007 - Antiseizure Prophylaxis, Bourdeaux et al. 2011,Brodie 1997, Bulger et al. 2010 Chang and Lowenstein 2003, Clifton et al. 2001 CRASH trial collaborators 2004, Cottenceau et al. 2011 Crash 2 Collaborators 2011, 2005 Gabriel et al. 2002 - Brain-targeted therapy, Georgiu et al. 2013, Harris et al. 2002, Langham et al. 2004, Narayan et al. 2008, Piek et al. 1992, Roberts 2004 a, Roberts 2004 b, Roberts und Schierhout 2009, Roberts und Sydenham 2012, Schierhout and Roberts 2004, Villalobos et al. 1998, Wakai et al. 2013 Willis et al. 2004, Yannagawa et al. 2004]

8. BESONDERHEITEN - PROGNOSE

In der Frühphase nach Schädelhirntrauma kann die Prognose in der Regel auch durch den Geübten nur mit großer Ungenauigkeit abgeschätzt werden. Als wesentliche Faktoren von fundamentaler prognostischer Bedeutung haben sich die Bewusstlosigkeit und begleitende neurologische Störungen, die Dauer der Bewusstlosigkeit und das Alter erwiesen . Unter den Zusatzuntersuchungen kommt den evozierten Potenzialen eine hohe prognostische Bedeutung zu. Die Lokalisation von Hirnschädigungen im Kernspintomogramm, besonders des Hirnstammes, ist ebenfalls bedeutsam für die Prognose.

Eine häufig übersehene Spätfolge nach SHT ist die **hypophysäre Insuffizienz** . Bei Verdacht sollte eine endokrinologische Abklärung erfolgen. Bei älteren und prädisponierten Patienten kann es auch nach relativ leichter Gewalteinwirkung mit mehrwöchiger Latenz zur Ausbildung einer intrakraniell raumfordernden Blutung, eines chronischen subduralen Hämatoms, kommen.

[Firsching et al. 2001, Frowein and Firsching 1990, Kelly et al 2000, Lieberman et al 2001, Schneider et al 2006]

NACHBEHANDLUNG

E45	**B**	**Bei Patienten, bei denen eine Kraniektomie durchgeführt wurde, sollte aus kosmetischen aber auch aus funktionellen Gesichtspunkten (Schutz des unterliegenden Gewebes) eine operative Deckung des Kalottendefektes erfolgen. Empfehlungen zum optimalen Zeitpunkt und zum operativen Verfahren können aus der derzeitigen Literatur nicht abgeleitet werden.**

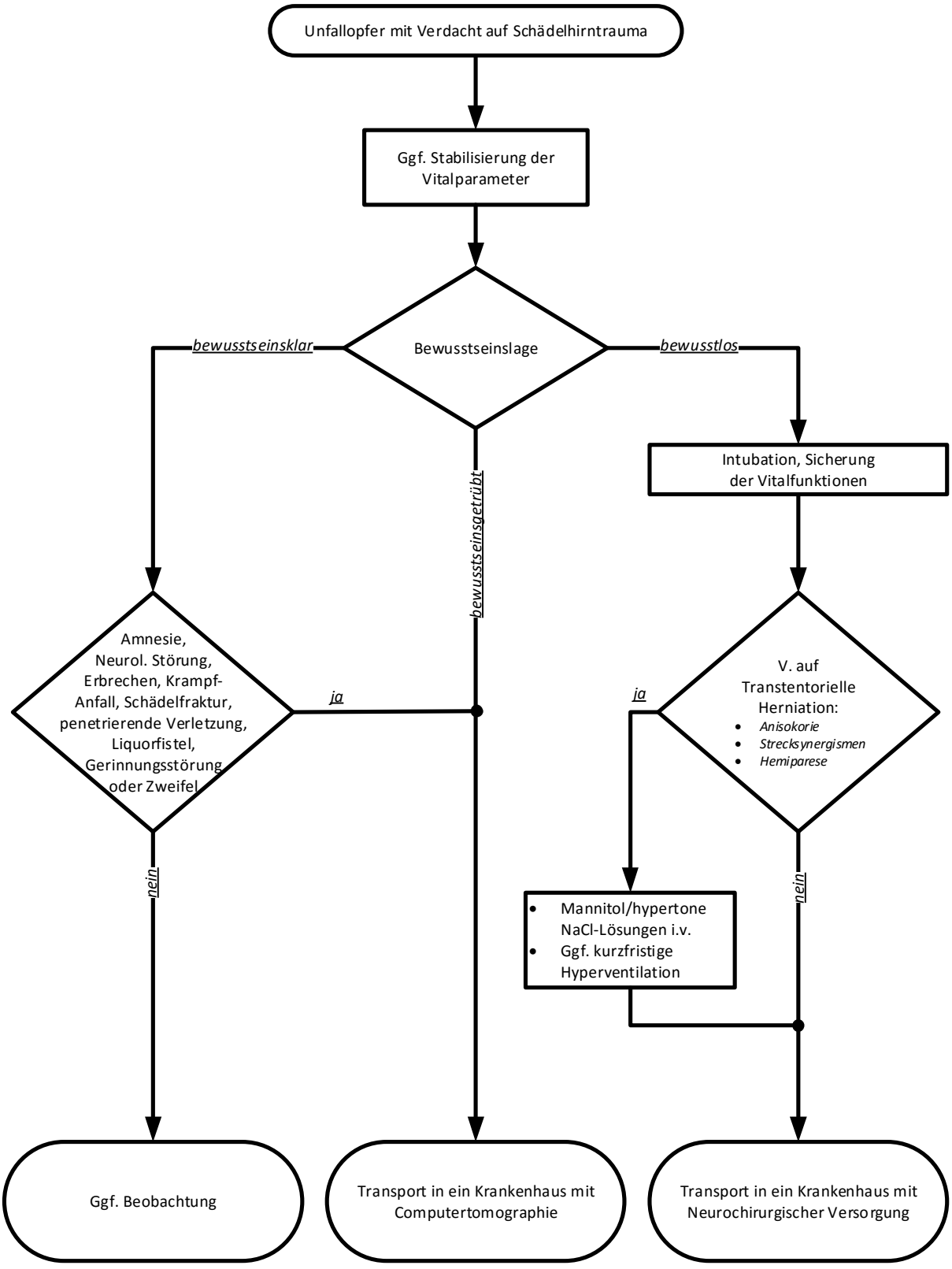
Eine Kranioplastie zur Deckung des Kalottendefektes nach Kraniektomie ist nicht nur aus kosmetischen Gründen sinnvoll, sondern auch aufgrund ihres schützenden Effektes auf das unterliegende Hirngewebe. Insbesondere im Rahmen der Rehabilitation bei zwar zunehmend mobileren, aber noch deutlich stand- und gangunsicheren Patienten mit dadurch erhöhter Sturzgefahr ist dieser Schutzeffekt von nicht zu unterschätzender Bedeutung. Darüber hinaus finden sich in der Literatur Hinweise darauf, dass es bei einem Teil der kraniektomierten Patienten aufgrund der veränderten pathophysiologischen Bedingungen zu sekundären neurologischen Beeinträchtigungen (u.a. verstärkten Kopfschmerzen, Zunahme von Paresen, Begünstigung epileptischer Anfälle) und zentral-vegetativen Regulationsstörungen kommen kann, dem sog. "Sinking Skin Flap"-Syndrom (z.B. Akins and Guppy 2008). Dies scheint insbesondere Patienten mit kontinuierlicher Liquorableitung (z.B. ventrikuloperitonealem Shunt) zu betreffen. Umgekehrt gibt es Berichte über eine kurzfristige Besserung

neurologischer und kognitiver Symptome nach Kranioplastie (Bijlenga et al. 2007), was für eine möglichst frühzeitige Deckung von Kalottendefekten nach Kraniektomie sprechen würde. Nichtsdestotrotz können Empfehlungen zum optimalen Zeitpunkt der Kranioplastie aus der derzeitigen Literatur nicht abgeleitet werden, so dass die Wahl des Zeitpunkts bei jedem Patienten eine individuelle Entscheidung bleibt (Archavlis and Carvi 2012). Im Einzelfall kann unter Abwägung medizinischer und ethischer Gesichtspunkte auch auf eine Kranioplastie verzichtet werden, wenn z.B. bei einem apallischen Patienten ohne begründete Aussicht auf Zustandsbesserung ein individueller Nutzen dieser Maßnahme nicht erkennbar ist.

Die Nachbehandlung richtet sich nach den verbleibenden neurologischen Störungen und den Heilungsaussichten. Verbesserungen der neurologischen Störungen werden zum größten Teil innerhalb der ersten 2 Jahre nach Trauma erreicht. Als pathophysiologische Grundlage des Erholungsprozesses werden funktionelle und strukturelle neuroplastische Adaptionsvorgänge angesehen. Man geht davon aus, dass diese Reorganisationsvorgänge durch gezielte Übungen beeinflussbar sind. Aus diesem Grunde und zur Vermeidung von Komplikationen (z.B. Kontrakturen) sollte bereits in der Akutphase mit rehabilitativen Maßnahmen (z.B. Physiotherapie) begonnen werden, auch wenn es hierfür bislang keine klare Evidenz gibt. Eine möglichst rasche Einleitung einer neurologisch-neurochirurgischen (Früh-)Rehabilitationsmaßnahme entsprechend der Schwere der Funktionsstörungen und des resultierenden Ressourcenbedarfs sollte angestrebt werden. Bezüglich der Rehabilitation wird auf die entsprechenden Leitlinien (z.B. Leitlinie "Multiprofessionale neurologische Rehabilitation" der DGN) verwiesen.

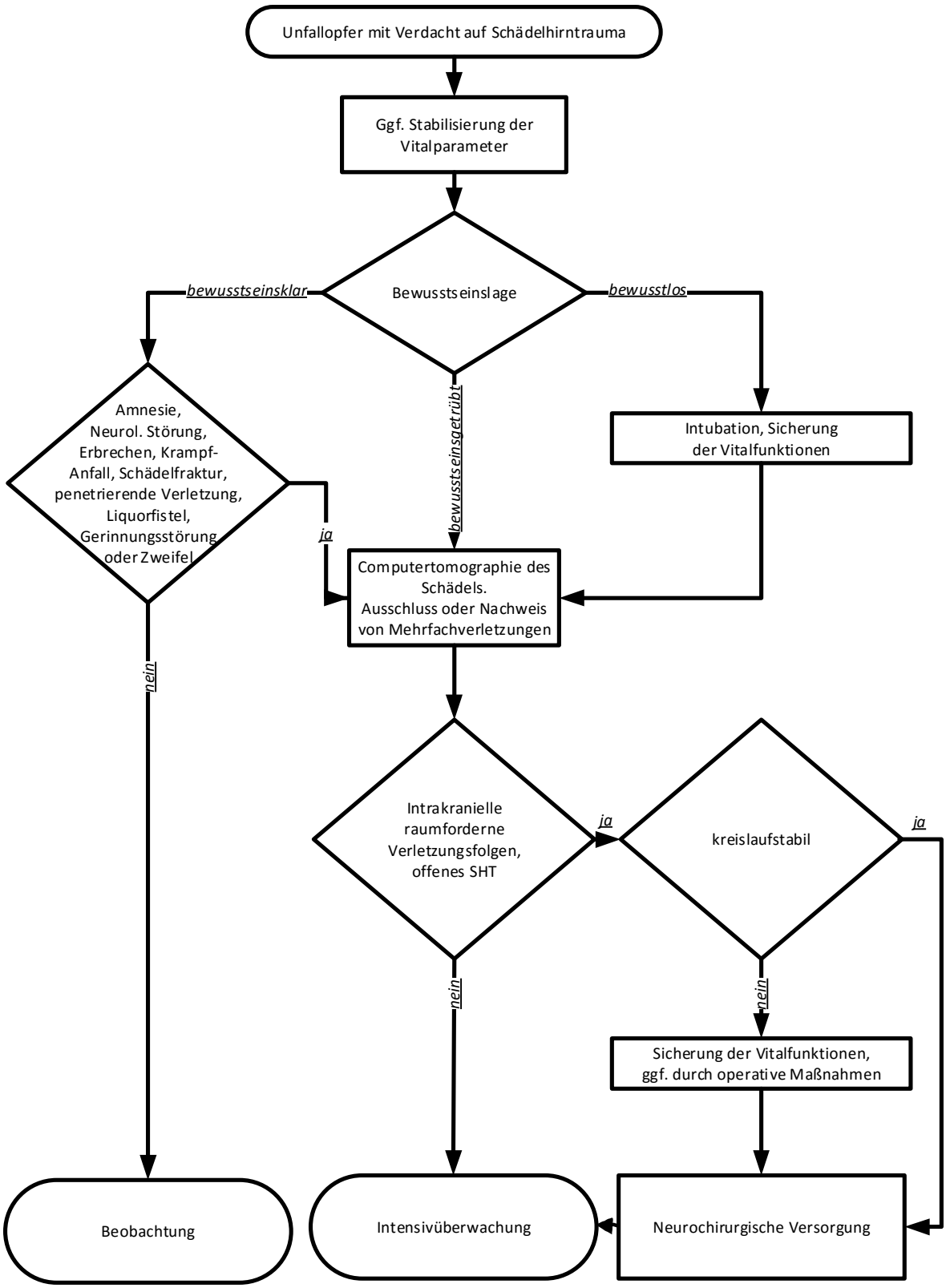
9. LEITLINIENALGORITHMEN

Behandlung des Patienten mit Schädel-Hirn-Trauma am Unfallort



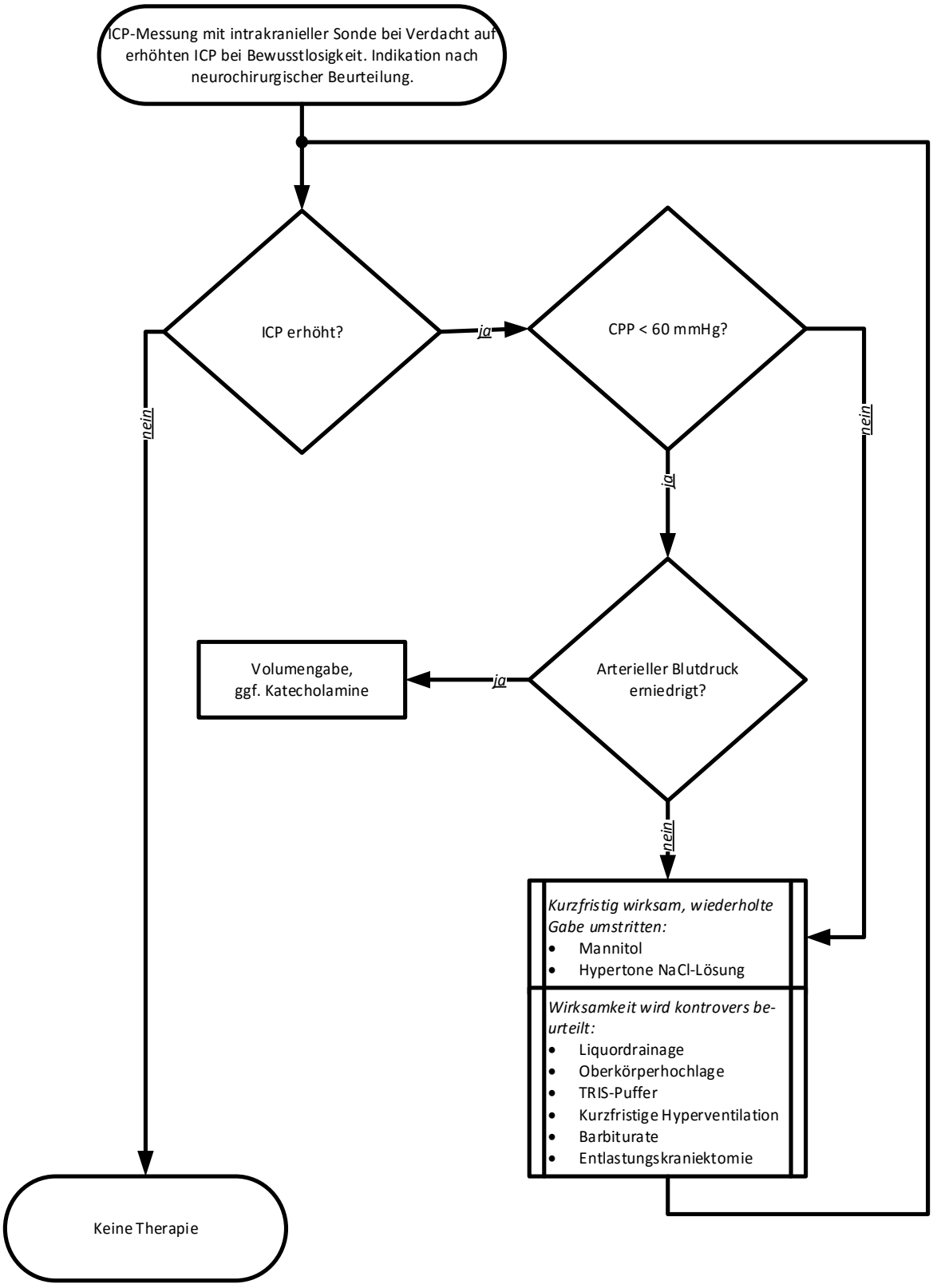
10.

Behandlung des Patienten mit Schädel-Hirn-Trauma im Krankenhaus



12.

Therapie des erhöhten intrakraniellen Drucks (ICP)



14.

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Anhang: "Evidenztabellen"

FRAGESTELLUNG UND ZUSAMMENFASSUNG DER ERGEBNISSE

Zur Vorbereitung des Updates dieser Leitlinie wurde eine Literaturrecherche der seit 2007 publizierten bzw. aktualisierten

- Systematischen Reviews einschließlich Cochrane Reviews,
- Metaanalysen,
- internationalen Leitlinien und
- randomisiert kontrollierten Studien (RCT)

durchgeführt. Die Trefferliste wurde bei den Sitzungen der Leitlinienarbeitsgruppe durchgearbeitet und auf relevante Publikationen eingeschränkt. Dies erfolgte in einem ersten Schritt auf Ebene der Titel und im zweiten Durchlauf nach Sichtung der Abstracts. Daraus ergaben sich folgende 11 Themenkomplexe, zu denen die Evidenz aus den vorliegenden Publikationen extrahiert wurde:

1. Präklinische Intubation

Aus dem RCT von Bernard et al. 2010 ergibt sich eine schwache Evidenz, die für eine präklinische Intubation bei SHT-Patienten mit einem GCS score ≤ 9 spricht.

2. Kortikosteroide

Der Cochrane Review, der nach der ersten Version unserer Publikation publiziert wurde, enthält keine neuen Informationen. Eine Änderung der Empfehlungen ist daher nicht erforderlich.

3. Intrakranieller Druck – ICP - Monitoring

Der Cochrane Review von Forsyth et al, der 2010 veröffentlicht wurde, enthält keine Daten aus RCTs, die die Bedeutung des ICP-Monitorings beim akuten traumatischen und nicht-traumatischen Koma klären. Der systematiche Review von Stein et al. (2010) zeigt einen leichten Vorteil für das ICP-Monitoring bei Patienten mit schwerem SHT. Es wurden jedoch hauptsächlich retrospektive Studien ausgewertet, sodass die Evidenz begrenzt ist. Relativ starke Evidenz enthält der RCT von Chesnut et al (2012), der jedoch keinen Vorteil des ICP-Monitorings zur Steuerung der ICP-Therapie zeigt. Dizdarevic et al.2011 verglichen eine ICP-gesteuerte Therapie (Lund - Konzept) mit einer Therapie, die durch den zerebralen Perfusionsdruck (CPP) gesteuert wird und sahen geringe Vorteile für das Lund - Konzept. Die Fallzahl, besonders beim SHT ist sehr klein, sodass die Schlussfolgerung mit Vorsicht zu sehen ist.

Zusammengefasst ergibt sich keine sicherer Hinweis für den Vorteil einer ICP-Messung, die als Monitoringoption anzusehen ist.

4. Ca-Blocker

Seit der ersten Version dieser Leitlinie ist keine relevante Publikation erfolgt. Der Cochrane Review zu diesem Thema wurde 2003 publiziert und bislang erfolgte keine substanzielle Ergänzung.

5. Hämostatika

Im Kontrast zum Polytrauma, bei dem ein lebensrettender Effekt der Tranexamsäure nachgewiesen wurde, gibt es keine verlässliche Evidenz für die Wirkung hämostatisch wirkender Medikamente beim SHT.

6. Hyperventilation

Der Cochrane Review zu diesem Thema wurde 1997 veröffentlicht und 2009 aktualisiert. Eine Änderung der Schlussfolgerungen ergab sich nicht.

7. Barbiturate.

Der Cochrane Review zu diesem Thema wurde 1996 veröffentlicht und 2012 aktualisiert. Lediglich eine neue Studie wurde aufgenommen, die jedoch keine neuen Informationen erbrachte. Eine Änderung der Empfehlung ist nicht erforderlich.

8. Entlastungskraniektomie

Obwohl alle Studien und Reviews eine ICP-senkende Wirkung der Entlastungskraniektomie zeigen, ist bislang kein Vorteil für den klinischen Outcome mit adäquater Evidenz nachgewiesen worden.

9. Hypothermie

Der von Saxena et al 2008 publizierte Cochrane Review fand keine adäquate Studie für die Analyse. In der Zwischenzeit gibt es zwei qualitative hochwertige Studien mit widersprüchlichen Ergebnissen. Cooper et al (2008) fanden einen klaren Vorteil für die Hypothermie während Georgiou et al 2013 dies nicht bestätigen konnte. Der letztere Review umfasst neuere Publikation und auch sehr viel mehr Patienten, sodass ihm eine größere Bedeutung zugemessen werden muss. Zwei weitere RCTs (Lee et al. 2010, Harris et al. 2009) beziehen sich auf metabolische Aspekte und enthalten keine Daten zum klinischen Outcome. Zusammengefasst gibt es aktuell keine klare Evidenz für den Nutzen der Hypothermie beim SHT

10. Mannitol/Hypertone Kochsalzlösung

Weiterhin gibt es keine klare Evidenz für den Nutzen von Mannitol oder hypertoner Kochsalzlösung beim SHT. Aus pathophysiologischen Überlegungen und aufgrund der nachweisbaren, oft temporären Senkung erhöhten intrakraniellen Drucks, kann die Anwendung beim Mittelhirnsyndrom bzw. Zeichen der transtentoriellen Herniation gerechtfertigt werden. Es scheint keine Unterschiede im Effekt von Mannitol und hypertoner Kochsalzlösung zu geben.

11. CT-Indikation

Der Review von Pandor et al. (2012) bestätigt bekannte Faktoren, die auf eine Hirnschädigung, insbesondere eine intrakranielle Blutung bei initial leichteren Formen des SHT hindeuten. Der systematische Review von Under und Romnen (2010) impliziert, dass S100B bei diesen SHT-Patienten die Durchführung eines CCT triggern könnte. Der gepoolte negative Vorhersagewert von 99% ist sehr überzeugend. Jedoch wurden in dem Review überwiegend Studien mit mittlerem Evidenzniveau ausgewertet. Die Veröffentlichung von Ding et al (2012) betont erneut den Wert der standardmäßig wiederholten CCT-Untersuchung. Die methodische Qualität dieser Studie ist allerdings sehr niedrig.

Eine tabellarische Zusammenstellung der Publikationen und der für die Evidenzbewertung relevanten Parameter finden sich in den folgenden Tabellen.

1 PREHOSPITAL INTUBATION

1.1 COCHRANE-REVIEWS

Not found

1.2 SYSTEMATIC REVIEWS

not found

1.3 RCTs

Author(s)/ Title	Bernard SA, Nguyen V, Cameron P, Masci K, Fitzgerald M, Cooper DJ, Walker T, Std BP, Myles P, Murray L, David, Taylor, Smith K, Patrick I, Edington J, Bacon A, Rosenfeld JV, Judson R. Prehospital rapid sequence intubation improves functional outcome for patients with severe traumatic brain injury: a randomized controlled trial. Ann Surg. 2010 Dec;252(6):959-65. doi: 10.1097/SLA.0b013e3181efc15f. PubMed PMID: 2110710		
Study type	Multicentre-RCT		
Intervention(s)	prehospital rapid sequence intubation by paramedics	**control**	transport to a hospital emergency department for intubation by physicians
a priori subgroups	• patients with an initial Glasgow Coma Score ≥5, • patients aged ≤60 years, • patients with an EMS transport time greater than 20 minutes to the trauma hospital.		
Inclusion criteria	• Evidence of head trauma, • Glasgow Coma Score ≤9, • age ≥15 years, • intact airway reflexes.	**exclusion criteria**	• within 10 minutes of a designated trauma hospital, • no intravenous access, • allergy to any of the RSI drugs (as stated by relatives or a medical alert bracelet), • transport planned by medical helicopter.
Patients for Intervention(s)	n=160	**Patients for control**	n=152
Cross over/ protocol violations	Crossover from control to intubation n=8	**recruiting period**	April 2004 - January 2008

Primary Outcome:	At 6 months following injury, surviving patients or their next of-kin were interviewed by telephone using a structured questionnaire and allocated a score from 1 (deceased) to 8 (normal) using the extended Glasgow Outcome Scale (GOSe). Attempts to contact missing patients or their relatives were undertaken … up to 12 months postinjury. Patients who were unable to be contacted after this time were considered lost to follow-up	**Secondary Outcome:**	• 6-month GOSe divided into 2 groups: unfavorable (GOSe scores, 1–4) and favourable (GOSe scores, 5–8), • the duration of intensive care unit and hospital stay, • survival to hospital discharge.
Power analysis	the sample size was calculated to detect a change of 1 point in the median GOSe. The sample size estimate was increased by 20% to account for non-normality of the data and loss to follow-up. This resulted in a sample size of 312 patients to achieve 80% power at an alpha error of 0.05.	**population size**	According to power analysis, both arms are balanced concerning baseline characteristics.
randomisation process	Eligible patients were randomized by the attending paramedic opening an opaque, sealed envelope that indicated treatment allocation. The allocationwas computer randomized and allocated in blocks of 10 to each paramedic ambulance unit	**Intention-to-treat**	yes
follow-up/ drop-out	6 months/ loss to follow-up: intervention N=3, control n=10	**blinding**	the interviewer who made the assessment of outcome at 6 months was blinded to treatment allocation
flowchart	yes	**Adverse events/ complications**	Not reported
Statistics/ confidence intervals	yes	**CoI/ disclosure**	Not reported
Main results primary outcome	Median GOSe (IQR) • Intervention 5 (1−6) • control: 3 (1−6) • P=0.28		
Results secondary out-	Good neurologic outcome (GOSe 5−8) • intervention: 80/157 (51%) • control: 56/142 (39%) • P = 0.046, risk ratio, 1.28; 95% confidence interval, 1.00–1.64		

come	Age ≤60 yr and GOSe 5−8 • Intervention: 75/121 (62%) • control: 54/105 (51%) • P =0.094 Age >60 yr and GOSe 5−8 • intervention 5/35 (14%) • control: 2/35 (6%) • P =0.23 Transport time ≥20 min and GOSe 5−8 • Intervention 48/97 (50%) • control: 33/87 (38%) • P =0.12 Initial GCS 5−9 and GOSe 5−8 • Intervention 45/81 (57%) • control: 34/73 (47%) • P =0.27 Survival at hospital discharge • Intervention 107 (67%) • control: 97 (64%) • P =0.57		
Conclu clu-sions	In adults with severe TBI, prehospital rapid sequence intubation by paramedics increases the rate of favorable neurologic outcome at 6 months compared with intubation in the hospital.		
LoE	**2b**	**Rea-sons for down-grad-ing/ ex-clusion**	Downgraded as the conclusion is based upon only one secondary outcome

1.4 SUMMARY

There is some weak evidence for the benefit of prehospital intubation in TBI-patients with a GCS score ≤ 9

2 CORTICOSTEROIDS

2.1 COCHRANE-REVIEWS

Author(s)/ Title	Alderson P, Roberts I. Corticosteroids for acute traumatic brain injury. Cochrane Database of Systematic Reviews 2005, Issue 1. Art. No.: CD000196. DOI: 10.1002/14651858.CD000196.pub2.		
Study types included	All randomised controlled trials of corticosteroid use in acute traumatic brain injury	**Search period/ databases**	CENTRAL (The Cochrane Library 2007, Issue 4),MEDLINE (Ovid SP), PubMed , EMBASE (Ovid SP) and PsycINFO (Ovid SP). The searches were last updated in January 2008
search algorithm:	The search strategies used for previous versions of this review are listed in Appendix 1. The strategies used for the update can be found in Appendix 2.		
Inclusion criteria	• People of all ages with clinically diagnosed acute traumatic brain injury secondary to head injury who were treated with steroids or control within seven days of the injury. All severities of head injury were included. • RCTs • Adequate or better allocation concealment	**exclusion criteria**	Studies using a quasi random form of allocation were excluded from the review
Intervention(s)	corticosteroids (those steroids with predominantly glucocorticoid effects, namely prednisolone, betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone and triamcinolone) administered in any dose by any route for any duration started within seven days of the injury. Trials with these interventions were included irrespective of other treatments used	**control**	No corticosteroid therapy
Primary Outcome:	The major outcome data sought were numbers of deaths and numbers of people disabled at the end of the study period, using the Glasgow Outcome Scale (Jennett 1975) to assess the neurological outcome. The categories for persistent vegetative state and moderate disability were combined into 'disability' for this review.	**Secondary Outcome:**	We also extracted data on side effects or complications where these were reported, using the authors' definitions of these complications.
Selection of Studies	All randomised controlled trials of corticosteroid use in acute traumatic brain injury with adequate or unclear allocation concealment (according to the scale of Higgins 2008).		
Methods	• We calculated relative risks	**Alloca-**	Strategies for allocation concealment

(metaanalysis)	and 95%confidence intervals for mortality for each trial on an intention to treat basis. • Heterogeneity between trials was tested using a chi-squared test, where P less than or equal to 0.05 was taken to indicate significant heterogeneity. • As long as statistical heterogeneity did not exist, for dichotomous data, we calculated summary relative risks and 95% confidence intervals using a fixed-effect model.	**tion**	were extracted and evaluated
Blinding	Unclear in some studies	**Intention-to-treat**	yes
drop-out	Not reported	**Selective reporting**	Methodological quality was variable, so selective reporting cannot ruled out completely
Main results	• 20 trials with 12,303 randomised participants • The largest trial, with about 80% of all randomised participants, found a significant increase in the risk ratio of death with steroids 1.15 (95% CI 1.07 to 1.24) and a relative risk of death or severe disability of 1.05 (95% CI 0.99 to 1.10) • For infections the pooled risk ratio from five trials was 1.03 (95% CI 0.99 to 1.07) • the pooled risk ratio from the ten trials reporting gastrointestinal bleeding was 1.23 (95% CI 0.91 to 1.67)		
Conclusions	In the absence of a meta-analysis, we feel most weight should be placed on the result of the largest trial. The increase in mortality with steroids in this trial suggest that steroids should no longer be routinely used in people with traumatic head injury		
LoE	**1b**	**Reasons for downgrading/ exclusion**	downgraded as results were mainly influenced by the largest trial

2.2 SYSTEMATIC REVIEWS

not found

2.3 RCTs

not found

2.4 SUMMARY

The Cochrane review published since the first version of our TBI-guideline does not contain new information. So, no change of the corresponding recommendation is necessary

3 ICP

3.1 COCHRANE-REVIEWS

Author(s)/ Title	Forsyth RJ, Wolny S, Rodrigues B. Routine intracranial pressure monitoring in acute coma. *Cochrane Database of Systematic Reviews* 2010, Issue 2. Art. No.: CD002043. DOI: 10.1002/14651858.CD002043.pub2.		
Study types included	randomized controlled trials	**Search period/ databases**	We searched the Cochrane Injuries Group's Specialised Register (searched 7 April 2009), CENTRAL (The Cochrane Library 2009, Issue 1), MEDLINE 1950 to March week 4 2009, EMBASE 1980 to week 14 March 2009, CINAHL 1982 to March 2009, ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) 1970 toMarch 2009, Conference Proceedings Citation Index-Science (CPCI-S) 1990 to March 2009, PubMed (searched 7 April 2009, limit; added in last 6 months). The searches were last updated in April 2009.
search algorithm:	See Appendix 1.		
Inclusion criteria	• All randomised controlled studies of real-time ICP monitoring by invasive or semi-invasive means in acute coma (traumatic or nontraumatic aetiology) versus no ICP monitoring (that is, clinical assessment of ICP). • Patients with acute severe coma of traumatic or non-traumatic cause (severity defined by an admission GCS of less than or equal to 8). • Real-time ICP monitoring using any invasive or semi-invasive means. This includes: intraventricular catheters, subarachnoid space pressure transducers, serial lumbar or ventricular taps with ICP measurement.	**exclusion criteria**	Indirect estimations of ICP by imaging techniques (cranial CT, cranial ultrasound ± Doppler) will be excluded.
Intervention(s)	real-time ICP monitoring by invasive or semi-invasive means in acute coma (traumatic or nontraumatic aetiology)	**control**	versus no ICP monitoring (that is, clinical assessment of ICP)

Primary Outcome:	Primary outcome measures were all-cause mortality and severe disability at the end of the follow-up period.	**Secondary Outcome:**	Not reported
Selection of Studies	All randomised controlled studies of real-time ICP monitoring by invasive or semi-invasive means in acute coma (traumatic or nontraumatic aetiology) versus no ICP monitoring (that is, clinical assessment of ICP).		
Methods (metaanalysis)	no trial could be included	**Allocation**	no trial could be included
Blinding	no trial could be included	**Intention-to-treat**	no trial could be included
drop-out	no trial could be included	**Selective reporting**	no trial could be included
Main results	No studies meeting the selection criteria have been identified to date.		
Conclusions	There are no data from randomized controlled trials that can clarify the role of ICP monitoring in acute coma		
LoE	**0**	**Reasons for downgrading/ exclusion**	No evidence level as no trial could be included

3.2 Systematic Reviews

Author(s)/ Title	Stein SC, Georgoff P, Meghan S, Mirza KL, El Falaky OM.: Relationship of aggressive monitoring and treatment to improved outcomes in severe traumatic brain injury. J Neurosurg. 2010 May;112(5):1105-12. doi: 10.3171/2009.8.JNS09738		
Study types included	All kind of trials, mainly retrospective	**Search period/ databases**	Medline in January 2009 for English language publications on the outcome of severe TBI.
search algorithm:	not reported		
Inclu-	• The definition of “severe”	**exclu-**	not reported

sion criteria	followed historical usage; it was equated with coma before Glasgow Coma Scale scores were in common use, and equaled a score of ≤ 8 thereafter. • We included articles summarizing outcomes in case series containing at least 90 patients with severe closed TBIs.	**sion criteria**	
Intervention(s)	The patient groups with intracranial pressure (ICP) monitoring and intensive therapy	**control**	The patient groups without intracranial pressure (ICP) monitoring and intensive therapy
Primary Outcome:	Outcome variables we used were deaths and "favorable" outcomes (6-month Glasgow Outcome Scale scores of 4 or 5)	**Secondary Outcome:**	
Selection of Studies	see inclusion criteria We included case series in which deaths, but not other outcomes, were reported at hospital discharge or before 6 months.		
Methods (metaanalysis)	not reported	**Allocation**	not reported
Blinding	not reported	**Intention-to-treat**	not reported
drop-out	not reported	**Selective reporting**	not reported
Main results	• Although the mortality rate fell during the years reviewed, it was consistently ~ 12% lower among patients in the intense treatment group ($p < 0.001$). • Favorable outcomes did not change significantly over time, and were 6% higher among the aggressively treated patients ($p = 0.0105$).		
Conclu clusions	Aggressive ICP monitoring and treatment of patients with severe TBI is associated with a statistically significant improvement in outcome. This improvement occurs independently of temporal effects.		
LoE	**3a**	**Reasons for downgrading/ exclusion**	mainly base on retrospective series

3.3 RCTs

Author(s)/ Title	Chesnut RM, Temkin N, Carney N, Dikmen S, Rondina C, Videtta W, Petroni G, Lujan S, Pridgeon J, Barber J, Machamer J, Chaddock K, Celix JM, Cherner M, Hendrix T. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med. 2012 Dec 27;367(26):2471-81. doi: 10.1056/NEJMoa1207363. Epub 2012 Dec 12. PubMed PMID: 23234472; PubMed Central PMCID: PMC3565432.		
Study type	Multicenter-RCT		
Intervention(s)	The pressure-monitoring group had an intraparenchymal monitor placed as soon as possible and were treated to maintain an intracranial pressure of less than 20 mm Hg,	**control**	The care for patients randomly assigned to the imaging–clinical examination group was provided in accordance with a protocol based on the pretrial standard for care
a priori subgroups	no		
Inclusion criteria	• 13 years of age or older • GCS of 3 to 8 (GCS motor component of 1 to 5 if the patient was intubated) or a higher score on admission that dropped to the specifiedrange within 48 hours after injury	**exclusion criteria**	• GCS of 3 and bilateral fixed and dilated pupils • an injury believed to be unsurvivable.
Patients for Intervention(s)	n=157	**Patients for control**	n=167
Cross over/ protocol violations	only few, reported in the supplement	**recruiting period**	September 2008 -October 2011
Primary Outcome:	The primary outcome, assessed within 6 months after the study onset, was a composite of 21 components (see. text)	**Secondary Outcome:**	Protocol specified secondary outcomes were • the length of stay in the ICU and • systemic complications. post hoc secondary outcomes were • the hospital length of stay, • the number of days of mechanical ventilation, • treatment with high-dose barbiturates or • decompressive craniectomy, and • therapeutic intensity (see text)

Power analysis	yes	**population size**	Adequate, balanced
randomization process	randomization sequences were computer-generated by a data-center biostatistician and were stratified according to • site, • severity of injury (GCS score of 3 to 5, or GCS motor score of 1 to 2 if the patient was intubated, vs. GCS score of 6 to 8, or GCS motor score of 3 to 5 if the patient was intubated), and • age (<40 years vs. ≥40 years), with a block size of 2 or 4	**Intention-to-treat**	yes
follow-up/ drop-out	• 6 months • 8% Loss to follow-up	**blinding**	not possible
flowchart	no	**Adverse events/ complications**	described, no differences between arms
Statistics/ confidence intervals	adequate/yes	**CoI/ disclosure**	yes, in the supplement
Main results primary outcome	• Intervention: median 56 Interquartile range 22-77 • control: median 53 Interquartile range 21-76 • P = 0.49, POR 1.09 CI: 0.74-1.58		
Results secondary outcome	Protocol specified Length of stay in ICU — days • Intervention : Median 12, Interquartile range 6–17 • Control: Median 9, Interquartile range 6–16 • P = 0.25 POR 0.81 CI: 0.55-1.18 Length of stay in ICU with brain-specific treatment — days • Intervention : Median 3.4, Interquartile range 1.1–7.0 • Control : Median 4.8, Interquartile range 2.3–7.4 • P = 0.002 POR 1.87CI: 1.28–2.75 Posthoc: Integrated brain-specific treatment intensity		

	• Intervention : Median 69, Interquartile range 13–181 • Control : Median 125, Interquartile range 45–233 • P = <0.001 POR 2.36 CI: 1.60–3.47		
Conclu clu-sions	For patients with severe traumatic brain injury, care focused on maintaining monitored intracranial pressure at 20 mm Hg or less was not shown to be superior to care based on imaging and clinical examination. Post hoc analyses of integrated treatment intensity for increades ICP revealed that the total number of treatments was significantly higher in the control group despite the lack of ICP-monitoring.		
LoE	**1b**	**Rea-sons for down-grad-ing/ ex-clusion**	

Au-thor(s)/ Title	Dizdarevic K, Hamdan A, Omerhodzic I, Kominlija-Smajic E. Modified Lund concept versus cerebral perfusion pressure-targeted therapy: a randomised controlled study in patients with secondary brain ischaemia. Clin Neurol Neurosurg. 2012 Feb;114(2):142-8. doi: 10.1016/j.clineuro.2011.10.005. Epub 2011 Oct 28. PubMed PMID: 22036839.		
Study type	RCT concerning ICP vs CPP – targeted therapy Prospective observational study concerning cerebral microdialysis – not evaluated here		
Inter-ven-tion(s)	intracranial pressure-targeted therapy (ICP-targeted) with cerebral microdi-alysis (CM) with monitoring according to the modified Lund concept	**control**	cerebral perfusion pressure-targeted therapy (CPP-targeted).
a priori sub-groups	Subarachnoidal Hemorrhage vs TBI Three ages subgroups (unclear whether a priori) • I 16 - 35 yr • II 36 - 55 yr • III 56 – 70 yr		
Inclu-sion criteria	• Patients with SAH included those with ruptured aneu-rysms in the anterior circula-tion only, including those with multiple anterior circu-lation aneurysms. • Patients with severe TBI on-ly included those with iso-lated head injury and intra-dural focal lesions. TBI was classified as severe if pa-tients had Glasgow Coma Scale (GCS) ≤ 8.	**exclu-sion criteria**	• Patients with GCS 3 with or without brainstem reflexes, • significant co-morbidities, • posterior circulation aneurysms, • multisystem injuries and • diffuse axonal injuries were ex-cluded.
Pa-tients for In-tervention(s)	n=30 TBI 15	**Pa-tients for con-trol**	n=30 TBI 15
Cross	not mentioned	**recruit-**	January 2006 to June 2008

over/ protocol violations		**ing period**	
Primary Outcome:	Not exactly defined probably Glasgow outcome Scale at 12 months, however statistical analysis was only done for mortality	**Secondary Outcome:**	Not reported
Power analysis	not done	**population size**	Very small population, only 15 TBI-cases in the intervention and control group
randomization process	Patients…were randomised using a computer software into two groups according to postoperative treatment strategies	**Intention-to-treat**	Probably, not explicitely reported
follow-up/ drop-out	adequate/loss to follow-up 0%	**blinding**	Single blinded
flowchart	no	**Adverse events/ complications**	not reported
Statistics/ confidence intervals	Statistical analysis does not seem adequate Evaluation of a dichotomized variables by Mann-Whitney or paired t-test is not appropriate. Corresepondingly no confidence intervals are reported	**CoI/ disclosure**	All authors declared having no CoIs
Main results primary outcome	The mortality rate of patients receiving ICP-targeted therapy was significantly lower than those who received CPP-targeted therapy (20.0% versus 43.3%, P = 0.03).		
Results subgroups	• Comparisons of mortality rates between patients who had aneurysmal SAH or severe TBI after commencement of each allocated therapy revealed no statistical significance (P = 0.28 for ICP-targeted therapy; P = 0.36 for CPP-targeted therapy). • There was a tendency for increased mortality in patients from group age III as compared to those from group age I and II regardless of treatment strategy but this was not statistically significant (46.7% versus 26.7%, P = 0.35).		
Conclu clusions	The modified Lund concept, directed at bedside real-time monitoring of brain biochemistry by CM showed better results compared to CPP-targeted therapy in the treatment of comatose patients sustaining SBI (secondary brain injury) after aneurysmal SAH and severe TBI		

LoE	**3b**	**Reasons for downgrading/ exclusion**	very small sample size

3.4 SUMMARY

The Cochrane review by Forsyth et al, published in 2010 revealed no data from randomized controlled trials that can clarify the role of ICP monitoring in acute coma including patients with TBI. The systematic review by Stein et al. (2010) showed some benefit for using ICP-monitoring for patients with severe TBI, however, mainly retrospective series were evaluated, so the evidence is very limited. Rather strong evidence showing no benefit of ICP-monitoring arises from the RCT of Chesnut et al (2012). Dizdarevic et al. compared an ICP-driven therapy (Lund concept) with a CPP-targeted therapy and saw some advantages for the Lund concept. The sample size, especially concerning TBI is extremely small, so the conclusions should be discussed critically.

In summary there is no real evidence for the benefit of ICP-monitoring. It may be used as a monitoring option.

4 CA-BLOCKER

4.1 COCHRANE-REVIEWS

Author(s)/ Title	Langham J, Goldfrad C, Teasdale G, ShawD, Rowan K. Calcium channel blockers for acute traumatic brain injury. Cochrane Database of Systematic Reviews 2003, Issue 4. Art. No.: CD000565. DOI: 10.1002/14651858.CD000565.		
Study types included	Randomized controlled trials (RCTs) in patients with all levels of severity of clinically diagnosed acute traumatic brain injury.	**Search period/ databases**	• We searched the following electronic databases: • Cochrane Injuries Group's Specialised Register (up to November 2005); • Cochrane Central Register of Controlled Trials (The Cochrane Library, issue 4, 2005); • MEDLINE (1966 to November 2005); • EMBASE (1988 to November 2005); • Intensive Care National Audit & Research Centre's (ICNARC) database of RCTs (contains the results of the hand searching of 33 selected journals relevant to intensive care and emergency medicine); • Ottawa Stroke Trials Registry.
search algorithm:	#1 explode "Calcium-Channel-Blockers" / all SUBHEADINGS #2 (((calcium) near ((channel*) next (block* or inhibit* or antagonist*))) in TI) or (((calcium) near ((channel*) next (block* or inhibit* or antagonist*))) in AB) #3 ((verapimil* or nifedipine* or nicardipine* or amlodipine* or felodipine* or isradipine* or iacidipine* or nimodipine* or diltiazem*) in TI)or((verapimil* or nifedipine* or nicardipine* or amlodipine* or felodipine* or isradipine* or iacidipine* or nimodipine* or diltiazem*) in AB) #4 #1 or #2 or #3 #5 explode "Brain-Injuries" / all SUBHEADINGS in MIME,MJME #6 explode "Craniocerebral-Trauma" / all SUBHEADINGS in MIME,MJME #7 explode "Subarachnoid-Hemorrhage" / all SUBHEADINGS in MIME,MJME #8 (((head or crani* or capitis or brain* or forebrain* or skull* or hemisphere* or intracran* or orbit*) next (injur* or trauma* or lesion* or damag* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)) in TI) or (((head or crani* or capitis or brain* or forebrain* or skull* or hemisphere* or intracran* or orbit*) next (injur* or trauma* or lesion* or damag* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)) in AB) #9 (Subarachnoid near (hemorrhage or haemorrhage)) in TI) or ((Subarachnoid near (hemorrhage or haemorrhage)) in AB) #10 #5 or #6 or #7 or #8 or #9 #11 #4 and #10 #12 #11 and Cochrane HSSS phases 1-2		

Inclusion criteria	• Randomised controlled trials (RCTs). • Patients with clinically diagnosed acute traumatic brain injury, of any age and in any healthcare setting. • Patients with traumatic subarachnoid haemorrhage • Any calcium channel blocker (calcium antagonist), namely: verapamil, nifedipine, nicardipine, amlodipine, felodipine, isradipine, lacidipine, nimodipine and diltiazem, administered in any dose, by any route, for any duration, and at any time of onset	**exclusion criteria**	patients with spontaneous subarachnoid haemorrhage .
Intervention(s)	Any calcium channel blocker (calcium antagonist),	**control**	
Primary Outcome:	• total mortality; • an unfavourable outcome - defined as death, severe disability or persistent vegetative state as described by the Glasgow Outcome Scale (Jennett 1975).	**Secondary Outcome:**	• quality of life; • personality changes in adults; • disruption to family; • delayed development in children (for example, speech development); • physiological/biological measures (computerized axial tomography (CAT) scans, cerebral blood flow); • economic factors. • In addition, adverse side-effects of the treatment (for example, hypotension) were studied.
Selection of Studies	One author scanned all abstracts of all studies identified through electronic searching and retrieved the full text of relevant articles. Two authors (JL and CG) independently assessed the identified studies for eligibility. Any disagreements were discussed with a third review author (KR) until agreement was reached.		
Methods (metaanalysis)	We extracted the following data from each study: • the number of participants randomised to each group; • inclusion and exclusion criteria; • interventions; • outcomes measured; • number of participants lost to follow-up; • summary of the results. Summary odds ratios were calculated in RevMan software, using the Mantel-Haenszel method.	**Allocation**	Allocation concealment systematically assessed but not discussed with authors.

Blinding	Assessed by Jadad-scale	**Intention-to-treat**	Not reported
drop-out	Assessed by Jadad-scale	**Selective reporting**	An assessment of the methodological quality of each trial report was carried out using two validated scales (Downs 1996; Jadad 1996). Two authors (JL and CG) independently carried out this assessment. Any disagreements were discussed with a third author (KR) until consensus was reached.
Main results	• Six RCTs involving 1862 participants were included • The effect of calcium channel blockers on the risk of death was reported in five of the RCTs. The pooled odds ratio (OR) for the five studies was 0.91 (95% confidence interval [95% CI] 0.70 to 1.16). • For the five RCTs that reported death and severe disability (unfavourable outcome), the pooled OR 0.97 (95%CI 0.81 to 1.18). • In the two RCTs which reported the risk of death in a subgroup of traumatic subarachnoid haemorrhage patients, the pooled OR 0.59 (95% CI 0.37 to 0.94). • Three RCTs reported death and severe disability as an outcome in this subgroup, and the pooled OR 0.67 (95% CI 0.46 to 0.98		
Conclusions	This systematic review of randomised controlled trials of calcium channel blockers in acute traumatic head injury patients shows that considerable uncertainty remains over their effects. The effect of nimodipine in a subgroup of brain injury patients with subarachnoid haemorrhage shows a beneficial effect, though the increase in adverse reactions suffered by the intervention group may mean that the drug is harmful for some patients.		
LoE	**1a**	**Reasons for downgrading/ exclusion**	

4.2 Systematic Reviews

not found

4.3 RCTs

not found

4.4 Summary

No relevant publications dealing with this topic has been published since the first issue of our TBI-guideline. The Cochrane review was published in 2003 and no substantial amendment has been added.

5 HEMOSTATIC DRUGS

5.1 COCHRANE-REVIEWS

Author(s)/ Title	Perel P, Roberts I, Shakur H, Thinkhamrop B, Phuenpathom N, Yutthakasemsunt S. Haemostatic drugs for traumatic brain injury. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD007877. DOI: 10.1002/14651858.CD007877.pub2.		
Study types included	published and unpublished randomised controlled trials	**Search period/ databases**	We searched the electronic databases: • Cochrane Injuries Group Specialised Register (3 February 2009), CENTRAL (*The Cochrane Library* 2009, Issue 1), • MEDLINE (1950 to Week 3 2009), PubMed (searched 3 February 2009 (last 180 days)), • EMBASE (1980 to Week 4 2009), • CINAHL (1982 to January 2009), • ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to January 2009), • ISI Web of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to January 2009). We searched the Internet for relevant information and conference abstracts. We also sought other potentially relevant published, unpublished, or ongoing studies by: • checking the reference lists of relevant papers and literature reviews, • communicating with relevant trial authors, • contacting the manufacturers of relevant drugs.
search algorithm:	Depends upon the database searched – s. Appendix I		
Inclusion criteria	• Any patient with traumatic brain injury. • Any of the systemic haemostatic drugs listed below compared with placebo, no treatment, or another hae-	**exclusion criteria**	We identified a trial that evaluated the effects of aprotinin in patients with severeTBI. It was reported as a randomised controlled trial; however after randomly allocating the first 20 patients, five patients were added to the aprotinin group. It was not possible to separate the out-

	mostatic drug. • For studies in which different doses of the intervention were compared with placebo, the intervention groups were combined and compared with the control group. • For the purpose of this review, we considered the following haemostatic drugs. • Antifibrinolytics: o aprotinin, o tranexamic acid (TXA), o aminocaproic acid. • Activated factor VIIa.		come data for the 20 randomised and the five non-randomised patients. Therefore, this study provided no useable outcome data and was excluded
Intervention(s)	trials comparing haemostatic drugs (antifibrinolytics: aprotinin, tranexamic acid (TXA), aminocaproic acid or recombined activated factor VIIa (rFVIIa)) in patients with acute traumatic brain injury	**control**	with placebo, no treatment, or other treatment in patients with acute traumatic brain injury
Primary Outcome:	• Mortality • Disability o Glasgow Outcome Scale (GOS), o Disability Rating Scale (DRS), or o other measure of neurological function) • Thrombotic complications: o deep venous thrombosis (DVT), o pulmonary embolism (PE), o stroke and o myocardial infarction (MI)	**Secondary Outcome:**	• Volume of intracranial bleeding • Brain ischaemic lesions • Need for neurosurgical operation or reoperation • Renal failure
Selection of Studies	Two review authors (PP and IR) independently examined all electronic records and their abstracts to establish eligibility. They decided on whether or not to acquire the full report and, in cases of uncertainty, obtained the full report. We planned to resolve any disagreements through discussion and consultation with a third review author. Any duplicate trials were planned to be examined individually to verify that they presented unique sets of data. If we were unsure about whether a study should be included, because additional information was necessary, we allocated the study to the list of those awaiting assessment and contacted the study authors for clarification.		
Methods (metaanalysis)	Two review authors (PP and IR) extracted the data from the included studies. We extracted data on the study methods, participants, interventions, and outcomes. We extracted data so that an intention-to-treat analysis could be performed. For binary outcomes, we determined	**Allocation**	Two review authors (PP and IR) evaluated the risk of bias of the included studies with respect to six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. The risk of bias in each domain was rated as high

	the number of participants experiencing the outcome of interest in each group. For continuous outcomes, we used the mean change from baseline at final assessment, together with the number of participants and standard deviation for each group. For dichotomous data, we calculated the risk ratio (RR) and 95% CI. We calculated the mean difference (MD) and 95%CI for continuous outcomes that were measured on the same scale, otherwise we planned to calculate the standardised mean difference.		risk, low risk, and unclear. Any disagreement between raters was resolved by consensus. We planned to assess reporting bias using a funnel plot.
Blinding	See Allocation	**Intention-to-treat**	See Allocation
drop-out	See Allocation	**Selective reporting**	See Allocation
Main results	• two trials • The risk ratio for mortality at 30 days was 0.64 (95% CI 0.25 to 1.63) for rFVIIa compared to placebo in the first study (post-hoc – analysis) • The other trial evaluated the effect of rFVIIa in 97 TBI patients with evidence of intracerebral bleeding in a computed tomography (CT) scan. The corresponding risk ratio for mortality at the last follow up was 1.08 (95% CI 0.44 to 2.68).		
Conclu clusions	There is no reliable evidence from randomised controlled trials to support the effectiveness of haemostatic drugs in reducing mortality or disability in patients with TBI.		
LoE	**2a**	**Reasons for downgrading/ exclusion**	due to the very low quality of the two studies included)

5.2 SYSTEMATIC REVIEWS

not found

5.3 RCTs

Author(s)/ Title	CRASH-2 Collaborators, Intracranial Bleeding Study. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study). BMJ. 2011 Jul 1;343:d3795. doi: 10.1136/bmj.d3795. PubMed PMID: 21724564; PubMed Central PMCID: PMC3128457

Study type	RCT		
Intervention(s)	loading dose of 1 g tranexamic acid infused over 10 minutes, followed by an intravenous infusion of 1 g over eight hours	**control**	Matching placebo (sodium chloride 0.9%).
a priori subgroups	no		
Inclusion criteria	• 13 years of age or older • GCS of 3 to 8 (GCS motor component of 1 to 5 if the patient was intubated) or • a higher score on admission that dropped to the specified range within 48 hours after injury	**exclusion criteria**	• GCS of 3 and bilateral fixed and dilated pupils • an injury believed to be unsurvivable.
Patients for Intervention(s)	n=133	**Patients for control**	n=137
Cross over/ protocol violations	Protocol deviations were as follows: • nine (3%) patients were randomised before the first computed tomography (six allocated tranexamic acid, three controls); • 31 (11%) had a Glasgow coma scale of 15 at baseline (17 allocated tranexamic acid, 14 controls); and • in 51 (19%) the second computed tomography was conducted outside the 24–48 hours window (25 allocated tranexamic acid, 26 controls).	**recruiting period**	between August 2008 and January 2010
Primary Outcome:	The primary outcome was total haemorrhage growth, defined as the difference in the combined volume (mL) of all intracranial haemorrhagic lesions (intra-parenchymal haematoma + haemorrhagic contusion + subdural haematoma + epidural haematoma) from the first to the second scan.	**Secondary Outcome:**	Secondary outcomes were • significant haemorrhage growth defined as an increase by ≥25% of total haemorrhage in relation to its initial volume, • new intracranial haemorrhage (apparent on the second scan but not apparent on the first), • change in subarachnoid haemorrhage grade, • mass effect, and • new focal cerebral ischaemic lesions (apparent on the second scan but not the first).

			The clinical outcomes were • death from any cause, • dependency, • and the need for neurosurgical intervention. Clinical outcomes were recorded at hospital discharge, at 28 days after randomisation, or death, whichever occurred first. Dependency was measured using the five point modified Oxford handicap scale (mOHS).17 We dichotomised the scale into "dependent" (fully dependent requiring attention day and night, or dependent but not requiring constant attention) or independent" (some restriction in lifestyle but independent, minor symptoms, or no symptoms). We also reported a "composite poor outcome" defined as a patient who developed one or more of the following during the follow-up period—significant haemorrhage growth, new intracranial haemorrhage, new focal cerebral ischaemic lesions, the need for neurosurgery, or death.
Power analysis	Yes Assuming an initial intracranial haemorrhage volume of 20 mL, an average haemorrhage growth of 7 mL in the control group and a correlation of 0.6 between initial and follow-up volumes, we estimated that a trial with 300 patients would have 80% power (α=0.05) to detect a 35% reduction in haemorrhage growth. We prespecified in the protocol that, as this study was nested within the main CRASH-2 trial, even if the planned sample size of 300 patients was not achieved, recruitment would stop at the same time as the main CRASH-2 trial.	**population size**	Adequate, balanced
randomization process	Not described – eventually see CRASH-2 main study	**Intention-to-treat**	yes
follow-up/ drop-out	We obtained two brain computed tomograms for each participant, the first before randomisation and the second 24–48 hours later which seems to be adequate for the primary outcome chosen. Clinical outcomes were recorded at hospital discharge, at 28 days after randomisation, or death, whichever occurred first. For clinical outcome the	**blinding**	Double-blinded

	time span is too short. Loss to follow-Up intervention : 8%, control 8%		
flowchart	no	**Adverse events/ complications**	No emergency unblinding was needed, and there were no adverse events regarded as serious, unexpected, or suspected to be related to the study treatment.
Statistics/ confidence intervals	adequate/yes	**CoI/ disclosure**	fully declared by all authors. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The Writing Committee had full access to all data in the study and had final responsibility for the decision to submit for publication
Main results primary outcome	The mean total haemorrhage growth was 5.9 mL (SD 26.8) and 8.1 mL (SD 29.2) in the tranexamic acid and placebo groups respectively. The adjusted analysis showed a reduction in total haemorrhage growth in the tranexamic acid group in comparison with the controls of –3.8 mL (95% confidence interval –11.5 to 3.9, P=0.33)		
Results secondary outcome	• In the tranexamic acid and placebo groups respectively, significant haemorrhage growth occurred in 44 (36%) and 56 (44%) patients, • new haemorrhage areas occurred in 13 (11%) and 20 (16%), • signs of mass effect occurred in 58 (47%) and 76 (60%), • and new focal cerebral ischaemic lesions occurred in six (5%) and 12 (9%) • The change in the subarachnoid haemorrhage scale was –0.11 for patients allocated tranexamic acid and –0.12 for control patients (P=0.93). • There were 14/133 (11%) deaths in the tranexamic acid group and 24/137 (18%) in the placebo group (adjusted odds ratio 0.47 (95% confidence interval 0.21 to 1.04, P=0.06). • Among the survivors, a total of 26/119 (22%) patients in the tranexamic acid group and 29/113 (26%) in the placebo group were dependent at hospital discharge or 28 days (adjusted odds ratio 0.66 (0.32 to 1.36, P=0.26). • twenty (15%) of the 133 patients in the tranexamic acid group and 21/137 (15%) in the placebo group had neurosurgery other than those evacuations based on first brain scan findings (adjusted odds ratio 0.98 (0.45 to 1.93) P=0.95). • Sixty (45%) patients in the tranexamic acid group and 80 (58%) in the placebo group had a “composite poor outcome” (adjusted odds ratio 0.57 (0.33 to 0.98) P=0.04).		
Conclu clusions	This trial shows that neither moderate benefits nor moderate harmful effects of tranexamic acid in patients with traumatic brain injury can be excluded		
LoE	**1b**	**Reasons for downgrading/ exclusion**	
Author(s)/	Narayan RK, Maas AI, Marshall LF, Servadei F, Skolnick BE, Tillinger MN; rFVIIa Traumatic ICH Study Group. Recombinant factor VIIA in traumatic intracerebral hemorrhage: results of a dose-escalation		

Title	clinical trial. Neurosurgery. 2008 Apr;62(4):776-86; discussion 786-8. doi: 10.1227/01.neu.0000316898.78371.74. PubMed PMID: 18496183		
Study type	randomized, double-blind, multicenter, placebo-controlled, dose-escalation trial		
Intervention(s)	Five dosages of rFVIIa (40, 80, 120, 160, and 200 µg/kg) were compared with placebo in escalating dose tiers. The first dose tier (40 µg/kg) consisted of 24 subjects randomly assigned in a 1:1 ratio to the treatment or placebo group. Subsequent dose tiers consisted of 18 subjects (2:1 for rFVIIa versus placebo), for a total of 96 planned patients. However, an additional patient was randomly assigned and received a dose in the 120 µg/kg rFVIIa dose tier, resulting in a total trial population of 97 patients.	**control**	placebo
a priori subgroups	none		
Inclusion criteria	• Patients older than the age of 18 years • with a history of a traumatic brain injury, • a Glasgow Coma Scale (GCS) score between 4 and 14, • and clinical evidence of tICH on their admission CT scan were considered for random assignment. • Subjects were randomly assigned into the trial if a contusion with a total volume of at least 2 ml was evident on the baseline CT scan obtained within 6 hours of the injury.	**exclusion criteria**	• were the presence of penetrating head or spinal cord injury, • life expectancy of less than 24 hours after hospital admission, • any planned surgical evacuation of intracerebral hematoma within 24 hours after dosing, • isolated subarachnoid hemorrhage, • intraventricular hemorrhage, • epidural or subdural hematomas or sICH, • significant cardiovascular disease or dysfunction, • hemodynamic instability, • known history of hypercoagulability or • thromboembolism, • current vitamin K antagonist use, • and pregnancy
Patients for Intervention(s)	n=61	**Patients for control**	n=36
Cross over/ protocol vio-	no	**recruiting period**	between August 2004 and May 2006

lations			
Primary Outcome:	The end points for this trial focused primarily on the safety of rFVIIa use, as determined by the occurrence of • AEs, • serious adverse events (SAEs), • predefined potential thromboembolic AEs, • and mortality within the 15-day trial period	**Secondary Outcome:**	Preliminary effectiveness was determined on the basis of changes in hematoma volume from baseline to 24 and 72 hours after dosing, as measured by centralized reading of the CT scans.
Power analysis	not done	**population size**	Probably too small
randomization process	not described	**Intention-to-treat**	yes
follow-up/ drop-out	15-day/ no information about drop-out	**blinding**	no
flowchart	yes	**Adverse events/ complications**	Primary outcome
Statistics/ confidence intervals	Adequate/yes	**CoI/ disclosure**	Declared, but no details are given
Main results primary outcome	• No significant differences were detected in mortality rate or number and type of adverse events among treatment groups. • TEs occurred in 6% (2 of 36) of the placebo-treated group and 16% (10 of 61) of the rFVIIa-treated groups (odds ratio [OR], 3.3; 95% confidence interval [CI], 0.69–16.2), with no dose-related trends across rFVIIa treatment groups. • There was one DVT in the placebo treatment group and five DVTs in the rFVIIa-treated group (OR, 3.1; 95% CI, 0.35–27.8).		
Results secondary outcome	• The mean tICH volume was greater across all treatment groups at 24 hours compared with baseline. • The mean overall change in tICH volume (24 h from the baseline CT scan) was 10.4 ml for placebo and 7.0 ml for all rFVIIa dose groups. Within the rFVIIa treatment groups, there was a nonsignificant trend for a rFVIIa dose-related limitation of tICH volume change		
Conclu clu-	In this first prospective study of rFVIIa in tICH, there appeared to be less hematoma progression in rFVIIa-treated patients (80–200 µg/kg) compared with that seen in placebo treated patients. The poten-		

sions	tial significance of this biological effect on clinical outcomes and the significance of the somewhat higher incidence of ultrasound-detected deep vein thromboses in the rFVIIa-treated group need to be examined in a larger prospective randomized clinical trial		
LoE	**2b**	**Reasons for downgrading/ exclusion**	low quality RCT underpowered possible bias by CoI

5.4 SUMMARY

In contrast to major trauma in which a life-saving effect of tranexamic acid could be shown there is no reliable evidence that TBI-patients may profit from hemostatic drugs

6 HYPERVENTILATION

6.1 COCHRANE-REVIEWS

Author(s)/ Title	Roberts I, Schierhout G. Hyperventilation therapy for acute traumatic brain injury. Cochrane Database of Systematic Reviews 1997, Issue 4. Art. No.: CD000566. DOI: 10.1002/14651858.CD000566.		
Study types included	randomized trials	**Search period/ databases**	We searched the following electronic databases; • CENTRAL (*The Cochrane Library* 2007, Issue 4); • MEDLINE (Ovid SP) 1950 to Nov (week 2) 2007; • PubMed [www.ncbi.nlm.nih.gov/ sites/entrez/] • Jan 2008: added to PubMed in the last 60 days); • EMBASE (Ovid SP) 1980 to (week 1) Jan 2008; • PsycINFO (Ovid SP) 1806 to April 2007; • We also conducted a general Internet search and searched webbased trials databases. • The reference lists of all relevant articles identified were checked. • A letter was sent to the first author of reports to ask for further information on the published report and asking them to assist in identifying any further trials which may have been conducted by them, or other investigators.
search algorithm:	Depends upon the database searched – s. Appendix I and Appendix II (update)		
Inclusion criteria	The review included all randomised and quasi-randomised controlled trials of hyperventilation in which hyperventilation was compared to normoventilation Trials in which participants had a clinically defined brain injury of any severity.	**exclusion criteria**	
Intervention(s)	The experimental intervention was hyperventilation ($PaCO_2$ less than or equal to 35mmHg) at any time within	**control**	Normoventilation

	eight weeks following injury.		
Primary Outcome:	We aimed to extract number of patients in the treatment and control groups who had died at the end of follow-up, who were in a vegetative state, severely disabled, moderately disabled or who had made a good recovery according to Glasgow Outcome Scale (GOS) criteria	**Secondary Outcome:**	
Selection of Studies	The review included all randomised and quasi-randomised controlled trials of hyperventilation in which hyperventilation was compared to normoventilation.		
Methods (metaanalysis)	Both reviewers independently extracted data and then crosschecked the extracted data. Data on the number of patients with each outcome event were extracted according to treatment allocated, regardless of whether or not the patient was subsequently deemed ineligible for follow-up or treatment, in order to allow an 'intent-to-treat' analysis. Since there is evidence that the quality of allocation concealment particularly affects the results of studies both reviewers scored this quality on the scale used by Higgins: • No = trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth); • Unclear = trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories; • Yes = trials deemed to have taken adequate measures to conceal allocation (i.e. central randomisation; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment).	**Allocation**	See Methods
Blinding	See Methods	**Intention-to-treat**	See Methods
drop-out	See Methods	**Selective re-**	See Methods

		porting	
Main results	• One trial of 113 participants was identified. • Hyperventilation alone, as well as in conjunction with a buffer (THAM [tris-hydroxymethyl-amino methane]), showed a beneficial effect on mortality at one year after injury, although the effect measure was imprecise (RR 0.73; 95% CI 0.36 to 1.49, and RR 0.89; 95% CI 0.47 to 1.72 respectively). • This improvement in outcome was not supported by an improvement in neurological recovery. • For hyperventilation alone, the RR for death or severe disability was 1.14 (95% CI 0.82 to 1.58). • The RR for death or severe disability in the hyperventilation-plus-THAM group was 0.87 (95% CI 0.58 to 1.28)		
Conclusions	The data available are inadequate to assess any potential benefit or harm that might result from hyper-ventilation in severe head injury.		
LoE	**1b**	**Reasons for down-grading/ exclusion**	(downgraded since only one RCT could be included)

6.2 Systematic Reviews

not found

6.3 RCTs

not found

6.4 Summary

The Cochrane report initially published in 1997 was actualized in 2009, however, its conclusion remained unchanged.

7 BARBITURATES

7.1 COCHRANE-REVIEWS

Author(s)/ Title	Roberts I, Sydenham E. Barbiturates for acute traumatic brain injury. Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD000033. DOI: 10.1002/14651858.CD000033.pub2.		
Study types included	Randomised controlled trials	**Search period/ databases**	TheCochrane InjuriesGroup'sTrials SearchCoordinator searched the following electronic databases; • CENTRAL (*The Cochrane Library* 2012, Issue 9); • MEDLINE (Ovid SP) 1950 to September Week 2 2012; • PubMed [www.ncbi.nlm.nih.gov/ sites/entrez/] (last searched 26 September 2012: added to PubMed in the last 60 days); • EMBASE (Ovid SP) 1980 to 2012 Week 38; • PsycINFO (Ovid SP) 1806 to September Week 3 2012; • PsycEXTRA (Ovid SP) 1908 to September 10, 2012; • ISI Web of Science: Science Citation Index (SCI) 1970 to Sept 26, 2012; • ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) 1990 to Sept 26, 2012.
search algorithm:	The search strategy used for the first version of the review which was published in 1997 can be found in Appendix 1. The search strategy used for this update can be found in Appendix 2. New trials were sought by checking the reference lists of the included trials, and review articles found through the literature search. We contacted authors of the included trials (both in 1996 during preparation of the original manuscript and again in November 2012) and asked if they were aware of any ongoing studies.		
Inclusion criteria	People with a clinically diagnosed acute traumatic brain injury of any severity.	**exclusion criteria**	
Intervention(s)	The experimental intervention comprised one or more of the barbiturate class of drugs (amobarbital, barbital, hexobarbital, mephobarbital, methohexital, murexide, pentobarbital, phenobarbital, secobarbital, thiobarbiturate).	**control**	The comparison could be standard care, placebo, or another barbiturate drug.
Primary Out-	Death at final follow-up	**Sec-**	Death or disability at final follow-up

come:		**ondary Out-come:**	(measured by the Glasgow Outcome Scale) • Intracranial pressure during treatment • Hypotension during treatment • Body temperature during treatment
Selection of Studies	The two review authors independently screened the search results, and then met to discuss the trials eligible for inclusion. There were no disagreements on the inclusion of trials.		
Methods (metaanalysis)	We extracted all outcome data, including side effects, the time the outcome measurements were taken, and the number of participants available to provide outcome data. The Glasgow Outcomes Scale score was converted into a dichotomous outcome according to the following standard grouping: 'Death or disability' included death, persistent vegetative state and severe disability, a 'good outcome' included moderate disability and good recovery. The two review authors independently extracted study data and checked the data included in the analyses to ensure there were no errors. There were no disagreements during data extraction or 'Risk of bias' assessment. The risk ratio with 95%confidence intervals was calculated for dichotomous outcomes. The mean difference with 95% confidence intervals was calculated for continuous outcomes which used the same scale. The difference between study groups at final follow-up was calculated. We contacted the study authors in order to obtain missing data. Trials testing barbiturate therapy against a control group were pooled separately from studies testing barbiturate therapy against another treatment. Statistical heterogeneity was assessed through the Chi^2 test, with a P value less than 0.10 indicating differences between study results which warrant further investigation. An I^2 test value over 50% also indicated considerable statistical heterogeneity. A Mantel-Haenzel fixed-effect model was used for the analysis in order to find the average effect of barbiturate drugs in the included trials.	**Allocation**	Information on the risk of bias were recorded including the method of randomization, generation of the randomization sequence and concealment of the sequence, blinding of patients, physicians and outcome assessors, incomplete outcome data and mention of a study protocol. Both review authors independently assessed the risk of bias for each study using The Cochrane Collaboration's 'Risk of bias' tool (*Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8.5)). We contacted the study authors for clarification of study methods and to ask for the study protocol. In 2012 we contacted the study authors to ask for their study protocol. We received replies but did not receive any original protocols due to the fact the studies were conducted 20-30 years ago. There are too few studies to include in a funnel plot to assess publication bias.

Blinding	See Allocation	**Intention-to-treat**	See Allocation
drop-out	See Allocation	**Selective reporting**	See Allocation
Main results	• Data from seven trials involving 341 people are included in this review • For barbiturates versus no barbiturate, the pooled risk ratio (RR) of death from three trials was 1.09 (95% confidence interval (CI) 0.81 to 1.47). • Death or disability, measured using the Glasgow Outcome Scale was assessed in two trials, the RR with barbiturates was 1.15 (95% CI 0.81 to 1.64). • Two trials examined the effect of barbiturate therapy on ICP. In one, a smaller proportion of patients in the barbiturate group had uncontrolled ICP (68% versus 83%); the RR for uncontrolled ICP was 0.81 (95% CI 0.62 to 1.06). • In the other, mean ICP was also lower in the barbiturate group. Barbiturate therapy results in an increased occurrence of hypotension (RR1.80; 95% CI 1.19 to 2.70). • For every four patients treated, one developed clinically significant hypotension. Mean body temperature was significantly lower in the barbiturate group. • In one study of pentobarbital versus mannitol there was no difference in death between the two study groups (RR 1.21; 95% CI 0.75 to 1.94). • Pentobarbital was less effective than mannitol for control of raised ICP (RR 1.75; 95% CI 1.05 to 2.92). • In one study the RR of death with pentobarbital versus thiopental was 1.78 (95% CI 1.03 to 3.08) in favour of thiopental. • Fewer people had uncontrollable ICP with thiopental (RR 1.64; 95% CI 1.03 to 2.60). • There was no significant difference in the effects of pentobarbital versus thiopental for death or disability, measured using the Glasgow Outcome Scale (RR 1.31; 95% CI 0.88 to 1.94), or hypotension (RR 0.95; 95% CI 0.81 to 1.12).		
Conclusions	There is no evidence that barbiturate therapy in patients with acute severe head injury improves outcome		
LoE	**1a**	**Reasons for downgrading/ exclusion**	

7.2 Systematic Reviews

not found

7.3 RCTs

not found

7.4 Summary

The Cochrane report initially published in 1996 was actualized in 2012 adding one new trial, however, its conclusion remained unchanged

8 DECOMPRESSIVE CRANIECTOMY

8.1 COCHRANE-REVIEWS

Author(s)/ Title	Sahuquillo J. Decompressive craniectomy for the treatment of refractory high intracranial pressure in traumatic brain injury. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD003983. DOI: 10.1002/14651858.CD003983.pub2.		
Study types included	Randomized or quasi-randomized studies	**Search period/ databases**	The search was not restricted by language or publication status. We searched the following databases: • Cochrane Injuries Group Specialised Register (searched 28May 2008); • CENTRAL (*The Cochrane Library* 2008, Issue 2); • PubMed (to 29 May, 2008, last 60 days); • MEDLINE (to May 2008); • EMBASE (to May 2008); • ZETOC (The British Library's Electronic Table of • Contents of current journals and conference proceedings (searched 29 May 2008); • Cumulative Index of Nursing and Allied Health (CINAHL) (to May 2008); • Controlled Trials *meta*Register (www.controlled-trials.com/mrct/ search) (searched 29 May 2008); • Neurobase (an additional proprietary database owned by the Neurotraumatology Research Unit, containing approximately 50,000 records on neurocritical care (March 2008). We also used the following Internet resources: • Clinical Practice Guidelines (www.guidelines.gov); • Google Scholar (http://scholar.google.com). searched the following databases to identify any ongoing or planned clinical trials: • Clinicaltrials.gov (www.clinicaltrials.gov); • Trials Central (www.trialscentral.org). When a

			clinical trial was detected, we contacted the principal investigator for further details. In addition to checking the reference lists of eligible articles, one of the authors (FA) handsearched the following books: • Intracranial Pressure, Volumes I (1972) to XII (2002); • Brain Edema. Proceedings of the Brain Edema international symposiums, from the VI International Symposium, November 1984, Tokyo to the last published proceedings (XI Brain Edema • International Symposium, June 1999, Newcastle-upon-Tyne). We contacted researchers known to be interested or involved in this type of procedure to identify any clinical trials that have not yet been published, or older trials that have never been published.
search algorithm:	Details of the search strategies used can be found in Appendix 1.		
Inclusion criteria	Patients over the age of 12 months with a severe traumatic brain injury and in a coma (post-resuscitation Glasgow Coma Scale score below or equal to eight points) and who underwent S-DC to control raised ICP that was refractory to medical treatment (analgesia, sedation, muscular paralysis, hyperosmolar solutions, hyperventilation, barbiturates, etc.) were included in this review. Because cerebrospinal fluid (CSF) drainage was considered as a first-level therapeutic measure in the second version of the 'Guidelines for the Management of Severe Head Injury' this maneuver was included as a conventional medical treatment. As in the first published version of this review only those studies that defined the type of lesion using a CT scan and in which ICP was monitored (regardless of the method) were included.	**exclusion criteria**	Studies that estimated ICP from the CT scans (diffuse unilateral or bilateral brain swelling, compressed basal cisterns, etc.) or neurological worsening in the absence of ICP monitoring were excluded.
Intervention(s)	In this systematic review, secondary decompressive craniectomy (S-DC)was defined as bone decompression with the dura mater left closed, scarified, open, or opened and augmented by duraplasty. The importance of opening the rigid and inelastic duramater in any decom-	**control**	Because this type of surgery has generally been carried out as a rescue therapy, clinical trials comparing decompressive surgery versus a control therapy are likely to be uncommon. If such studies were located, patients receiving maximal medical treatment would be considered the control group.

	pressive procedure was clearly stated by Cushing, in 1905. Several experimental and clinical studies of the craniospinal dynamics have emphasized this point and, therefore, studies that performed large bone decompression without opening the dura mater, although included in this review, were considered as suboptimal.		Maximal medical treatment is defined as non-surgical therapies used to control ICP (that is hyperosmolar solutions, sedation and paralysis, hyperventilation, barbiturates, and moderate hypothermia). Cerebrospinal fluid drainage in patients undergoing ICP-monitoring by ventriculostomy would also be considered as non-surgical therapy.
Primary Outcome:	The main outcome measures for this systematic review were as follows: • mortality at one month after injury (30 ± 10 days); • neurological outcome at six or 12 months evaluated with the dichotomized Glasgow Outcome Scale (GOS) and categorized into good or bad outcomes. ○ Patients with a good recovery or moderate disability were included in the good outcome group ○ while those who were severely disabled, remained in a vegetative state, or died were included in the bad outcome group.	**Secondary Outcome:**	A secondary outcome measure was the effectiveness of surgical treatment in significantly reducing ICP, which was defined as an ICP of less than 20 mm Hg after decompression. In studies reporting mean ICP a reduction of at least 10 mm Hg was considered to be significant.
Selection of Studies	The review author examined titles, abstracts, and keywords of citations from electronic databases for eligibility. The full text of all relevant records was obtained and assessed to see whether the record met the pre-defined inclusion criteria. When in doubt, advice from the editorial team of the Cochrane Injuries Group was requested. Reasons for excluding clinical trials and manuscripts were documented.		
Methods (metaanalysis)	As defined in the protocol, data on the following variables were extracted from the selected studies: • age; • gender; • Glasgow Coma Scale score on admission; • type of lesion, defined by the CT scan (focal versus diffuse); • summarized ICP data; • time from injury to surgical decompression; • surgical procedure; • results of surgical decompression on ICP control; • mortality and morbidity assessed by the GOS.	**Allocation**	To assess the quality of the randomized controlled trials (RCTs) or quasi-randomized clinical trials, the following items were evaluated: • details of method of randomization; • independent assessment of outcomes; • number of patients lost to follow up; • appropriateness of control groups; and • analysis of results based on an intention-to-treat principle. The CONSORT algorithm was also used to assess the quality of the RCTs. As previously discussed, clinicians could not be blinded to the type of treatment the patient was allocated due to the nature of the intervention. Consequently, blinding was evaluated but was not used as a criterion for the quality of the trial. However, blinding of the evaluator was essential for a study to be considered of

			high quality. Although it was used in the first version of this review, Jadad's scale was not used in this update because its use has been discouraged by Cochrane Collaboration methodologists. Instead, we used the risk of bias tool recommended by Higgins and Altman and incorporated into the latest version of Review Manager.
Blinding	See Allocation	**Intention-to-treat**	See Allocation
drop-out	See Allocation	**Selective reporting**	See Allocation
Main results	• only one trial with 27 participants, conducted in a pediatric population • Decompressive craniectomy was associated with a risk ratio (RR) for death of 0.54 (95% CI 0.17 to 1.72) • and a RR of 0.54 (95% CI 0.29 to 1.01) for an unfavorable outcome (death, vegetative status, or severe disability 6 to 12 months after injury)..		
Conclu clusions	Only one study with a pediatric population. In this study decompressive craniectomy (tends to) reduce the risk of death and unfavorable outcomes		
LoE	**2b**	**Reasons for downgrading/ exclusion**	downgraded since only one RCTwith a small sample size could be included

8.2 SYSTEMATIC REVIEWS

Author(s)/ Title	Bor-Seng-Shu E, Figueiredo EG, Amorim RL, Teixeira MJ, Valbuza JS, de Oliveira MM, Panerai RB. Decompressive craniectomy: a meta-analysis of influences on intracranial pressure and cerebral perfusion pressure in the treatment of traumatic brain injury. J Neurosurg. 2012 Sep;117(3):589-96. doi: 10.3171/2012.6.JNS101400. Epub 2012 Jul 13		
Study types included	any study design with prospective or retrospective data	**Search period/ databases**	PUBMED: January 1995 to December 2010.
search algorithm:	Two independent observers (E.B. and R.L.O.A.) performed a systematic PubMed database search using the keywords "decompressive craniectomy," "cerebral decompression," "brain decompression," and "decompression craniotomy." These subject headings were also combined with "head injury," "head trauma," "traumatic brain injury," "intracranial pressure," and "cerebral perfusion pressure." Reference lists of recovered articles were examined for additional suitable papers. The "Related Articles" feature in PubMed was also used for all selected studies to maximize the probability of finding additional relevant studies. A third independent investigator (E.G.F.) resolved potential disagreement between the 2 independent observers as regarded study identification. The authors of selected articles were contacted by electronic mail to provide additional data not available in their publications. Unpublished data were provided by authors of selected papers who responded		

	positively to our request.		
Inclusion criteria	The inclusion criteria for relevant research studies were as follows: • 1) published manuscripts, • 2) original articles of any study design with prospective or retrospective data, • 3) patients with posttraumatic brain swelling and refractory intracranial hypertension, • 4) decompressive craniectom as a type of intervention, and • 5) availability of quantitative analysis of ICP and/or CPP estimations beforeand after decompressive craniectomy.	**exclusion criteria**	Exclusion criteria were as follows: • 1) incomplete data for quantitative analysis (abstracts only, review articles, and case reports), • 2) nonhuman models, • 3) elevated ICP not associated with TBI, and • 4) non-English publications. Care was taken to exclude articles with patients already used in other articles from the same institution to avoid corrupting the population sample.
Intervention(s)	decompressive craniectomy.	**control**	obviously no controlled studies.
Primary Outcome:	Primary outcomes were ICP decrease and/or CPP increase for assessing the efficacy of decompressive craniectomy.	**Secondary Outcome:**	The secondary outcome was the persistence of ICP reduction 24 and 48 hours after surgical decompression, as compared with preoperative levels.
Selection of Studies	Twenty-three studies were identified. Corresponding authors of 4 studies were contacted; however, only 1 replied and provided the requested data. Three studies were excluded because of incomplete data for quantitative analysis. Twenty studies (479 patients) assessed immediate pre- and postoperative ICP values. Eight of them were prospective clinical studies and the remainder were retrospective studies		
Methods (metaanalysis)	Two authors who were not involved in data collection (J.S.V. and M.M.O.) performed all statistical analysis. Data synthesis and analysis were performed using The Cochrane Collaboration review manager software RevMan version 4.2.8. For continuous variables, where continuous scales of measurement are used to assess the effects of treatment, the WMD was used with 95% CIs.	**Allocation**	not reported
Blinding	not reported	**Intention-to-treat**	not reported
drop-out	not reported	**Selective reporting**	not reported
Main results	• Postoperative ICP values were significantly lower than preoperative values immediately after decompressive craniectomy (weighted mean difference [WMD] −17.59 mm Hg, 95% CI −23.45 to −11.73, $p < 0.00001$)		

	• 24 hours after (WMD −14.27 mm Hg, 95% CI −24.13 to −4.41, p < 0.00001), • and 48 hours after (WMD -12.69 mm Hg95% CI −22.99 to −2.39, p < 0.0001). • Postoperative CPP was significantly higher than preoperative values (WMD 7.37 mm Hg, 95% CI 2.32 to 12.42, p < 0.0001)		
Conclu clu-sions	Decompressive craniectomy can effectively decrease ICP and increase CPP in patients with TBI and refractory elevated ICP. Further studies are necessary to define the group of patients that can benefit most from this procedure		
LoE	**3a**	**Rea-sons for down-grad-ing/ ex-clusion**	Includes mainly low quality studies

8.3 RCTs

Author(s)/ Title	Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, Kossmann T, Ponsford J, Seppelt I, Reilly P, Wolfe R; DECRA Trial Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med. 2011 Apr 21;364(16):1493-502. doi: 10.1056/NEJMoa1102077. Epub 2011 Mar 25. Erratum in: N Engl J Med. 2011 Nov 24;365(21):2040. PubMed PMID: 21434843.		
Study type	multicenter, randomized, controlled Decompressive Craniectomy (DECRA) trial		
Intervention(s)	Within the first 72 hours after injury, we randomly assigned patients either to undergo decompressive craniectomy plus standard care	**control**	Or standard care alone
a priori subgroups	no		
Inclusion criteria	• Patients were eligible for participation in the trial • if they were between the ages of 15 and 59 years • and had a severe, nonpenetrating traumatic brain injury. • score of 3 to 8 on the Glasgow Coma Scale • or Marshall class III (moderate diffuse injury on computed tomography [CT]).	**exclusion criteria**	• Patients were excluded if they were not deemed suitable for full active treatment by the clinical staff caring for the patient • or if they had dilated, unreactive pupils, • mass lesions (unless too small to require surgery), • spinal cord injury, • or cardiac arrest at the scene of the injury
Patients for Intervention(s)	n=73	**Patients for control**	n=82
Cross over/ protocol violations	• 5% • 18% late crossover according to protocol (delayed craniectomy in standard care group)	**recruiting period**	From December 2002 through April 2010
Primary Outcome:	• The original primary outcome was the proportion of patients with an unfavorable outcome, a composite of death, a vegetative state, or severe disability (a score of 1 to 4 on the Extended Glasgow Outcome Scale), as assessed with the use of a structured, validated telephone questionnaire19-22 at 6 months after injury.2	**Secondary Outcome:**	• Secondary outcomes were • Intracranial pressure measured hourly, • the intracranial hypertension index23 (defined as the number of end-hourly measures of intracranial pressure of more than 20 mm Hg divided by the total number of measurements, multiplied by 100), • the proportion of survivors with a score of 2 to 4 on the Ex-

	• After the interim analysis in January 2007, the primary outcome was revised to be the functional outcome at 6 months after injury on the basis of proportional odds analysis of the Extended Glasgow Outcome Scale		tended Glasgow Outcome Scale (defined as severe disability and requiring assistance in daily living activities), • the numbers of days in the ICU and in the hospital, a • and mortality in the hospital and at 6 months
Power analysis	yes	**population size**	adequate according to power analysis, There were imbalances in some baseline characteristics of the patients, particularly the proportion of patients without pupil reactivity at hospital admission
randomization process	we randomly assigned patients either … using an automated telephone system. Randomization was stratified according to center and the technique that was used to measure intracranial pressure (external ventricular drain or parenchymal catheter) in blocks of two or four patients.	**Intention-to-treat**	yes
follow-up/ drop-out	6 months The assigned trial treatment (craniectomy or standard care) was administered to 96% of all patients	**blinding**	Outcome measures were evaluated by telephone by three trained assessors who were unaware of study-group assignments.
flowchart	no	**Adverse events/ complications**	reported, not analysed
Statistics/ confidence intervals	Adequate/yes	**CoI/ disclosure**	Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.
Main results primary outcome	• Six months after injury, the primary outcome (functional assessment on the Extended Glasgow Outcome Scale) was worse in the craniectomy group than in the standard-care group (median score, 3 vs. 4; odds ratio for a worse functional outcome in the craniectomy group, 1.84; 95% confidence interval [CI], 1.05 to 3.24; P = 0.03) • After adjustment for prespecified covariates, the results were similar for the score on the Extended Glasgow Outcome Scale (adjusted odds ratio for a lower score in the craniectomy group, 1.66; 95% CI, 0.94 to 2.94; P = 0.08) and for the risk of an unfavorable outcome (adjusted odds ratio, 2.31; 95% CI, 1.10 to 4.83; P = 0.03).		
Results secondary outcome	• Intracranial pressure after randomization [mm Hg] I: 14.4±6.8 C: 19.1±8.9 p<0.001 • No. of hr of intracranial pressure >20 mm Hg — median (IQRI) I: 9.2 (4.4–27.0); C: 30.0 (14.9–60.0) p<0.001 • Intracranial hypertension index — median (IQR)‡ I: 11.5 (5.9–20.3) C: 19.9 (12.5–37.8) p<0.001 • Cerebral hypoperfusion index — median (IQR)§ I: 5.7 (2.5–10.2), C: 8.6 (4.0–13.8) p=0.03 • Days of mechanical ventilation — median (IQR) I: 11 (8–15) C: 15 (12–20) p<0.001		

	• Days of ICU stay — median (IQR) I: 13 (10–18); C. 18 (13–24) p <0.001 • Days of hospitalization — median (IQR) I: 28 (21–62) C: 37 (24–44) p= 0.82		
Conclusions	In adults with severe diffuse traumatic brain injury and refractory intracranial hypertension,early bifronto-temporoparietal decompressive craniectomy decreased intracranial pressure and the length of stay in the ICU but was associated with more unfavorable outcomes.		
LoE	**2b**	**Reasons for downgrading/ exclusion**	methodological weakness
Author(s)/ Title	Qiu W, Guo C, Shen H, Chen K, Wen L, Huang H, Ding M, Sun L, Jiang Q, Wang W. Effects of unilateral decompressive craniectomy on patients with unilateral acute post-traumatic brain swelling after severe traumatic brain injury. Crit Care. 2009;13(6):R185. doi: 10.1186/cc8178. Epub 2009 Nov 23. PubMed PMID: 19930556; PubMed Central PMCID: PMC2811943.		
Study type	prospective randomized clinical trial.		
Intervention(s)	Craniotomy was undergone for all patients from 2 to 24 hours (mean 5.8 hours) after admission, and randomized into two groups as follows: unilateral decompressive cranietomy group (n = 37)	**control**	unilateral routine temporoparietal craniectomy group as control group (n = 37)
a priori subgroups	no		
Inclusion criteria	• a history of TBI, • Glasgow Coma Scale (GCS) of 8 or less at admission, • and swollen hemisphere (43 left and 31 right, with midline shift >5 mm and contusions <25 ml and compressed basal cisterns) apparent on CT scans.	**exclusion criteria**	• Patients below the age of 18 years or above 65 years, • Multiply injured patients, • those with any previous disabling neurological disease, • intracerebral haematoma of more than 3 cm in diameter, • previous craniectomy, • extra-axial haematoma greater than 0.5 cm in thickness, s • spinal cord injury, p • penetrating brain injury, • fixed dilated pupils • and GCS score of 3 with no chance of survival
Patients for Intervention(s)	n= 37	**Patients for control**	n= 37
Cross over/	not reported	**recruiting pe-**	between 2000 and 2008

protocol violations		**riod**	
Primary Outcome:	• The temperature, heart rate, respiration rate and blood pressure, arterial oxygen saturation The data were recorded at every 12 hours for 7 days after craniotomy. • Continuous recording of ICP was applied in all patients for 96 hours with the ICP monitor system • Complications. Mainly inclusive of delayed intracranial hematoma, pulmonary infection, digestive tract hemorrhage, and electrolytes disorders. The data were recorded every 12 hours for 7 days, and every 24 hours for another 7 days after craniotomy. • (4) Glasgow Outcome Scale (GOS) scores, from 1 to 5 respectively, evaluated at one year followup after injury	**Secondary Outcome:**	no differentiation between primary and secondary outcome
Power analysis	not done	**population size**	rather small, sample size
randomization process	the patient was assigned to one of the following two groups …using a randomization table	**Intention-to-treat**	Not reported
follow-up/ drop-out	differs depending upon parameters analyzed. Clinical outcome was assessed 12 months after trauma/ loss to follow-up not reported	**blinding**	Allocation and randomization was concealed and the investigators were not aware to which group the patient would be assigned, and the allocation sequence was protected until assignment The physicians in charge of the patient were not involved in data collection, and the nursing staff and the surgical team were not aware of the patient's group assignment. A single trained assessor and the data analyzer were blind to the treatment group
flowchart	no	**Adverse events/ complications**	Part of the outcome evaluation
Statistics/	not systematically applied to all outcome parameters	**Col/ disclo-**	all authors reported having no conflict of interest

confidence intervals		**sure**	
Main results primary outcome	• There was no significant difference of abnormality of vital signs between the two groups • The mean ICP values of patients in the unilateral DC group at 24, 48, 72 and 96 hours after injury were significantly lower (about 30%) than those of the routine temporoparietal craniectomy group (15.19 ± 2.18 mmHg, 16.53 ± 1.53 mmHg, 15.98 ± 2.24 mmHg and 13.518 ± 2.33 mmHg versus 19.95 ± 2.24 mmHg, 18.32 ± 1.77 mmHg, 21.05 ± 2.23 mmHg and 17.68 ± 1.40 mmHg, respectively) • There was no evidence of severe complications related to DC. As shown above, the incidences of delayed intracranial hematoma and subdural effusion were higher in the unilateral DC than in the control group (21.6% and 10.8% versus 5.4% and 0, respectively, P = 0.041 and 0.040) • The mortality rates one month after craniotomy were 27% in the unilateral DC group as compared with 57% in control group (P = 0.010). According to the GOS scores one year after injury, significant difference in overall neurological outcomes between both groups was found. The difference of good neurological recovery (GOS score 4 to 5) between the unilateral DC group and control group was significant (56.8% versus 32.4%).		
Results secondary outcome	No differentiation between primary and secondary outcomes		
Conclu clusions	Although the application of DC in severe TBI is controversial and the population in the present study is small, our study demonstrated that unilateral DC had superiority in lowering ICP, reducing the mortality rate and improving neurological outcomes over routine temporoparietal craniectomy		
LoE	2b	**Reasons for downgrading/ exclusion**	low quality RCT due to a lot of methodological deficits

8.4 Summary

Although all studies/reviews showed that ICP effectively is lowered by decompressive craniectomy, a benefit in clinical outcome cannot be proven with adequate evidence.

9 HYPOTHERMIE

9.1 COCHRANE-REVIEWS

Author(s)/ Title	Saxena M, Andrews PJD, Cheng A.Modest cooling therapies (35ºC to 37.5ºC) for traumatic brain injury. CochraneDatabase of Systematic Reviews 2008, Issue 3. Art. No.: CD006811. DOI: 10.1002/14651858.CD006811.pub2.		
Study types included	randomised, controlled or placebo-controlled trials	**Search period/ databases**	
search algorithm:			
Inclusion criteria		**exclusion criteria**	
Intervention(s)		**control**	
Primary Outcome:		**Secondary Outcome:**	
Selection of Studies			
Methods (metaanalysis)		**Allocation**	
Blinding		**Intention-to-treat**	
drop-out		**Selective reporting**	
Main results	We were unable to find any randomised, placebo-controlled trials of modest cooling therapies after traumatic brain injury		

Conclu clu-sions			
LoE	0	**Rea-sons for down-grad-ing/ ex-clusion**	No study included

9.2 SYSTEMATIC REVIEWS

Au-thor(s)/ Title	Georgiou AP, Manara AR. Role of therapeutic hypothermia in improving outcome after traumatic brain injury: a systematic review Br J Anaesth. 2013 Mar;110(3):357-67. doi: 10.1093/bja/aes500. Epub 2013 Jan 25		
Study types includ-ed	randomized controlled trials in English	**Search period/ data-bases**	systematic search of the MEDLINE and EMBASE databases was conducted with medical librarian assistance from 1966 to July 28, 2011, Zetoc database of conference proceed-ings Cochrane Database of Systematic Re-views clinicaltrials.gov website
search algo-rithm:	• 'traumatic brain injury', 'traumatic brain injury hypothermia', and 'hypothermia intracranial pres-sure'. Filters were applied for clinical trials and review articles. • Additional searches were performed using the search term: 'hypothermia, induced [Mesh] and brain injuries [Mesh]' and 'induced hypothermia [Emtree] and traumatic brain injury [Emtree]'. • A search of the Zetoc database of conference proceedings was performed using the search term 'hypothermia traumatic brain injury'. • The Cochrane Database of Systematic Reviews was searched using the terms 'traumatic brain injury', 'traumatic brain injury hypothermia', and 'hypothermia intracranial pressure'. • search of the clinicaltrials.gov website was performed using the search term 'traumatic brain injury hypothermia'. • Executive researchers of relevant trials were contacted via e-mail for further information on their respective studies. • Relevant journals were hand-searched for further references. • Reference lists from selected articles and from review articles were then checked against the retrieved results for additional resources.		
Inclu-sion criteria	English language. (ii) Randomized controlled trial in patients with TBI. (iii) Use of induced systemic hypo-thermia for ≥12 h in the treatment arm. (iv) Assessment of survival and neu-rological outcome at a minimum of 3 months after injury.	**exclu-sion criteria**	Not reported

Intervention(s)	Use of induced systemic hypothermia for ≥12 h in the treatment arm.	**control**	normothermia
Primary Outcome:	A lot of parameters were extracted from the included studies. However, in the result section only mortality and neurological outcome (dichotomized Glasgow outcome score (GOS) in adults and dichotomized paediatric cerebral performance category (PCPC) in children) were addressed.	**Secondary Outcome:**	
Selection of Studies	The articles selected were assessed for quality of evidence by each author independently using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system of assessment. Eighteen randomized controlled trials were selected and are summarized in Table 1. The authors independently reached consensus as to the quality of each trial. The overall quality of the evidence was graded as low.		
Methods (metaanalysis)	Relevant data were extracted from each paper by hand and entered into a spreadsheet (Excel, Microsoft Corporation, Redmond, WA, USA). The power of each study and the relative risk of mortality and neurological outcome with respective confidence intervals were calculated if they were not presented in the paper. Forest and funnel plots were performed to facilitate data consolidation (RevMan 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The outcome from both fixed and random effects models were obtained in the meta-analysis;	**Allocation**	assessed
Blinding	assessed	**Intention-to-treat**	Not reported
drop-out	Not reported	**Selective reporting**	assessed
Main results	• Eighteen randomized controlled trials (1851 patients) were identified • The overall relative risk of mortality with PTH when compared with controls was 0.84 [95% confidence interval (CI)¼0.72–0.98] • and of poor neurological outcome was 0.81 (95% CI¼0.73–0.89). • However, when only high quality trials were analysed, the relative risks were 1.28 (95% CI¼0.89–1.83) and 1.07 (95% CI¼0.92–1.24), respectively.		
Conclu clusions	Given the quality of the data currently available, no benefit of PTH on mortality or neurological morbidity could be identified.		

LoE	**1a**	**Reasons for downgrading/ exclusion**	
Author(s)/ Title	Peterson K, Carson S, Carney N. Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis. J Neurotrauma. 2008 Jan;25(1):62-71. doi: 10.1089/neu.2007.0424.		
Study types included	randomized controlled trials in English	**Search period/ databases**	**Previous reviews:** January 1, 1966 through week 1 of September 2002. Searches in these reviews involved numerous electronic databases including MEDLINE (OVID), EMBASE, Cochrane Library, Current Contents (week 27 of year 1993 to week 40 of year 2002), abstract center for the American Association of Neurological Surgeons and the Congress of Neurological Surgeons, Science Citation Dissertation Abstracts, CENTRAL, and Specialist Trials Registry for the Injuries Group. **UPDATE** MEDLINE (2002 through June Week 4 2007)
search algorithm:	**Previous reviews:** Reference lists of four previous good-quality systematic reviews (Alderson et al., 2004; McIntyre et al., 2003; Harris et al., 2002; Henderson et al., 2003) provided the basis for identification of all eligible RCTs. They used various combinations of MeSH (Medical Subject Headings) terms and text words for hypothermia, brain injury, craniocerebral trauma, and neurosurgery. **Update** combining the following terms: "Brain Injuries," "hypotherm$," "(brain or cerebr$) adj3 temperature$." Filters for English language, human, and controlled trial were applied.		
Inclusion criteria	We included English-language publications of RCTs that compared the benefits and harms of hypothermia to standard care upon hospital admission in adults with TBI. Adult populations were defined as being comprised of at least 85% of patients aged 14 years or above.	**exclusion criteria**	
Intervention(s)	hypothermia	**control**	standard care
Primary Outcome:	**The primary effectiveness outcome** was all-cause mortality. **Subgroups:** Target cooling temperatures below 33°C were classified a priori as "moderate" and temperatures of 33°C and	**Secondary Outcome:**	The secondary effectiveness outcome was favorable neurological response, defined as the proportion of patients that achieved a Glasgow Outcome Scale score of 4 or 5 at various time points.

	above were classified as "mild." Cooling duration was analyzed using a prespecified cut-off of 48 h. Rewarming methods were classified as either "passive" or "active." ICP management strategies were classified based on use or nonuse of barbiturates. For trial duration, groups were defined as "3–6 months" and "1–2 years."		For safety, we examined rates of arrhythmia and pneumonia.
Selection of Studies	Two reviewers (K.P. and S.C.) independently assessed abstracts for inclusion using these criteria. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria. All disagreements were resolved through consensus.		
Methods (metaanalysis)	Two reviewers (K.P. and S.C.) independently abstracted data from the primary studies into an Excel spreadsheet using a prespecified form. Reviewers were masked to author and journal. Disagreements were resolved through consensus. For all variables, we calculated pooled relative risks (RR) and associated 95% confidence intervals (CIs) using random-effects models (Deeks, 1998). Statistical heterogeneity was calculated using the chi-squared test.	**Allocation**	Two reviewers (K.P. and S.C.) independently assessed the internal validity of individual trials using predefined criteria based on methods used for randomization and allocation concealment, between-groups similarity in baseline demographic and prognostic factors, blinding of outcome assessors, adequacy of sample size, use of intention-to-treat analysis, follow-up rates, and associated maintenance of comparable groups. The quality assessment tool was created based on criteria developed by the U.S. Preventive Services Task Force (Harris et al., 2001), the National Health Service Centre for Reviews and Dissemination (U.K.) (Centre for Reviews and Dissemination, 2001), and the Cochrane Collaboration (Higgins and Green, 2006). Internal validity raters were masked to author and journal. Disagreements were resolved by consensus and, in some cases, involved consultation with a third masked reviewer (N.C.). Results are depicted in Table 2
Blinding	see Allocation	**Intention-to-treat**	see Allocation
drop-out	see Allocation	**Selective reporting**	see Allocation
Main results	• main analyses were conducted based on eight trials that demonstrated the lowest potential for bias (n _ 781). • Reductions in risk of mortality were greatest (RR 0.51; 95% CI 0.33, 0.79) and • favorable neurologic outcomes much more common (RR 1.91; 95% CI 1.28, 2.85) when hypothermia was maintained for more than 48 h. • However, this evidence comes with the suggestion that the potential benefits of hypothermia may likely be offset by a significant increase in risk of pneumonia (RR 2.37; 95% CI 1.37, 4.10).		
Conclu	In sum, the present study's updated meta-analysis supports previous findings that hypothermic therapy constitutes a beneficial treatment of TBI in specific circumstances		

clusions			
LoE	**1a**	**Reasons for downgrading/ exclusion**	

9.3 RCTs

Author(s)/ Title	Lee HC, Chuang HC, Cho DY, Cheng KF, Lin PH, Chen CC. Applying cerebral hypothermia and brain oxygen monitoring in treating severe traumatic brain injury. World Neurosurg. 2010 Dec;74(6):654-60. doi: 10.1016/j.wneu.2010.06.019. PubMed PMID: 21492636.		
Study type	This clinical study was designed as a randomized, controlled trial		
Intervention(s)	after craniotomy…. • Group B (15 patients) was combined mild hypothermia and ICP/CPPguided management, • and Group C (14 patients) was combined mild hypothermia and PtiO2 guided with ICP/ CPP management on patients with severe TBI.	**control**	after craniotomy. • Group A (16 patients) was intracranial pressure/cerebral perfusion pressure (ICP/CPP)–guided management only,
a priori subgroups	no		
Inclusion criteria	• a history of TBI; • Glasgow Coma Scale (GCS) scores of 4–8; and • brain damage confirmed • by sequential computed tomography (CT) scanning within 6 hours after trauma.	**exclusion criteria**	• pregnant women; • patients younger than age 12 years or older than age 70 years; • a GCS score of 3; • multiply injured patients; and • 5) those with any previous disabling neurologic disease.
Patients for Intervention(s)	n(B) =15, n(C)=14	**Patients for control**	n(A)=16
Cross over/ protocol violations	not reported	**recruiting period**	during September 2006 and August 2007

Primary Outcome:	Clinical parameters
	• GOS
	  ○ good outcome >3
	  ○ good outcome >2
	• mortality
	• ICU stay
	• total stay
	monitoring parameter
	• mean ICP/d
	• high ICP/d
		Secondary Outcome:	no differentiation between primary and secondary outcome

Power analysis	not done	**population size**	rather small, sample size not calculated by power analysis, therapeutic arms were balanced for sex, age, GCS – score, initial ICP, CT-findings, percentage of craniotomy
randomization process	not described	**Intention-to-treat**	no
follow-up/ drop-out	6 months for clinical outcome, probably 5 days for ICP-measurement, no linformatkon concerning loss to follow-up	**blinding**	no
flowchart	no	**Adverse events/ complications**	reported with obviously no difference between therapeutic arms.
Statistics/ confidence intervals	Student's t test for unpaired results and, whenever necessary, the _2 test, one-way ANOVA, Fisher's exact test, repeated measures ANOVA, and Kruskal–Wallis test were used to compare measurements. Data were expressed as means±standard deviations. The squared deviations [measured as (daily observation - daily group mean)^2] were used to compare the daily variation of ICP. Statistical significance was set at P <0.05 and the Glasgow Outcome Scale (GOS) score was analyzed by measuring process capability (Cpk). The process of calculation of the Cpk-ration was not further specified. No confidence intervals were reported Statistics may not be adequate	**Col/ disclosure**	The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest
Main results	The ICP values progressively increased in the first 3 days but showed smaller changes in the hypothermia groups (Groups B and C) and were significantly lower than those of the normothermia group (Group		

primary outcome	A) at the same time point. Using repeated measures ANOVA in SAS software, we found out that the averaged ICP were significantly related to days. In addition, daily variations [measured as (daily observation - daily group mean)^2] of ICP were found to be significantly different among the three treatment groups after the third posttraumatic day The mean ICU stay was significantly longer in the hypothermia groups; they were 9 days in Group A, 11.33 days in Group B, and 11.6 days in Group C ($P < 0.05$). But the total hospital stay was much shorter in Group C (this, however, is not significant in the ANOVA) The Cpk values (medical treatment process capability) of Group C (Cpk_0.50) were of the greatest among them. The Cpk values of Group A and B were 0.35 and 0.46, respectively The percentage of favourable neurologic outcome was50%in the normothermia group, 60% in the hypothermia only group, and 71.4% in the PtiO2 group, respectively, with statistical significance. The percentage of mortality was 12.5% in the normothermia group, 6.7% in the hypothermia only group, and 8.5% in PtiO2 group, respectively, without statistical significance in these three groups.		
Results secondary outcome	no differentiation between primary and secondary outcome		
Conclu clusions	Therapeutic mild hypothermia combined with PtiO2-guided CPP/ ICP management allows reducing elevated ICP before 24 hours after injury, and daily variations of ICP were shown to be significantly different among the three treatment groups after the third posttraumatic day. It means that the hypothermia groups may reduce the ICP earlier and inhibit the elicitation of acute inflammation after cerebral contusion. Our data also provided evidence that early treatment that lowers PtiO2 may improve the outcome and seems the best medical treatment method in these three groups. We concluded that therapeutic mild hypothermia combined with PtiO2-guided CPP/ICP management provides beneficial effects when treating TBI,		
LoE	**2b**	**Reasons for downgrading/ exclusion**	due to the low sample size and the inadequate statistics

Author(s)/ Title	Harris OA, Muh CR, Surles MC, Pan Y, Rozycki G, Macleod J, Easley K. Discrete cerebral hypothermia in the management of traumatic brain injury: a randomized controlled trial. J Neurosurg. 2009 Jun;110(6):1256-64. doi: 10.3171/2009.1.JNS081320. Erratum in: J Neurosurg. 2009 Jun;110(6):1322. PubMed PMID: 19249933.		
Study type	a randomized, controlled design stratified on the extended head injury scale based on injury severity		
Intervention(s)	For patients assigned to the treatment group, the cooling cap was placed on the patient's head and secured around the neck. …..The system was set to maximum cooling, with a goal of reaching a target intracranial temperature of 33°C and remaining at this temperature for 24 hours.	**control**	Patients allocated to the control group did not receive a cooling cap.

a priori sub-groups	GCS score on initial assessment (severe [5–8] vs critical [3–4]),		
Inclusion criteria	• The patient was being treated for severe TBI, GCS score ≤ 8; • The patient was at least 18 years of age; • The patient required an ICP monitor and Foley catheter as part of routine treatment; • The patient was able to receive the Discrete Cerebral Hypothermia cooling cap within 48 hours of hospital admission; • The patient's family member or guardian spoke English to ensure proper informed consent; and • 6) The patient's family member or guardian agreed to participate and signed an informed consent.	**exclusion criteria**	• The patient's family member or guardian was unwilling or unable to sign an informed consent; • The physical placement of the cooling cap impeded routine treatment; • The patient's core body temperature was ≤ 36°C at the time of initial assessment; and • 4) Treatment could not be initiated within 48 hours of admission.
Patients for Intervention(s)	N=12	**Patients for control**	N=13
Cross over/ protocol violations	Not reported	**recruiting period**	from July 2006 until August 2007
Primary Outcome:	Our primary outcomes for this study were the effectiveness of the cooling cap in reducing the patient's internal brain temperature and in establishing a gradient between patients' core and brain temperatures following TBI.	**Secondary Outcome:**	The secondary objective was to perform a comparative analysis of outcome using mortality, GOS, and FIM scores following severe TBI.
Power analysis	Not done	**population size**	Very small, balanced for baseline characteristics except the length of stay in the emergency department with a significant longer stay in the control group
randomization process	The randomization was determined by the Department of Biostatistics using computer-generated random numbers. These numbers were assigned to each patient based on their order in the study and GCS score on initial assessment (severe [5–8] vs critical [3–4]), to allow for block randomization and to provide an initial balance in severity between the 2 groups	**Intention-to-treat**	yes

follow-up/ drop-out	Until discharge or 1 month for secondary outcomes/ The dropout process was assumed to be missing at random. (??)	**blinding**	no
flowchart	no	**Adverse events/ complications**	• Respiratory failure (18 patients [72.0%]), • shock (7 patients [28%]), • septicemia (6 patients [24%]), • decubitus ulcer (2 patients [8.0%]) • cardiac arrest (2 patients [8.0%]). There was no significant difference in complications between the groups;
Statistics/ confidence intervals	Adequate CI were calculated	**CoI/ disclosure**	The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.
Main results primary outcome	• Prior to initiating treatment, the estimated mean intracranial temperature for patients in the treatment group was 37.9°C (95% CI 37.4–38.5°C). After 12 hours of treatment with the cooling cap, the mean intracranial temperature had dropped to 36.8°C (95% CI 36.1–37.5°C). At the end of the 24-hour cap-on period, it was 36.9°C (95% CI 35.8–38.0°C). • In contrast, the mean intracranial temperatures for patients in the control group at baseline, 12 hours, and 24 hours were 37.9°C (95% CI 37.6–38.2°C), 37.9°C (95% CI 37.5–38.3°C), and 38.1°C (95% CI 37.7– 38.5°C), respectively. • After study Hour 3, the mean intracranial temperature of the treatment group was significantly lower than that of the control group ($p < 0.05$) at all time points except for Hours 4 ($p = 0.08$) and 6 ($p = 0.08$). • In 11 patients adequate data were available for assessing whether the target temperature was achieved; in only 2 o these 11 patients did we find that the target intracranial temperature of 33°C was achieved at any time during the cooling period • Overall, across the cooling period, the mean difference between intracranial and bladder temperature was −0.67°C ($p = 0.07$) for the treatment group and 0.05°C ($p= 0.67$) for the controls. This showed a trend toward a greater temperature gradient in the treatment group than in the controls However, the cooling cap neither established • nor maintained a significant cranial-bladder temperature gradient		
Results secondary outcome	• There was no significant intergroup difference in mortality rate or in time to death. • Therefore, there was no statistically significant intergroup difference in GOS determined morbidity. • Again, there was no significant difference between the study and control populations		
Conclu clusions	When this modality is subjected to intention-to-treat analysis, no significant benefits emerge. Though a future version of this technology may be successful at realizing the potential benefits of selective cerebral hypothermia, as it currently stands, this technology is not beneficial.		
LoE	**2b**	**Reasons for downgrading/ ex-**	Due to the very small sample size

		clusion	

9.4 Summary

The Cochrane Review published by Saxena et al in 2008 did not find any suitable trial for analysis of modest hypothermia (35-37.5°C). In the meantime there are two high-quality systematic reviews showing contradictory results for more aggressive systemic cooling. Cooper et al (2008) found a clear benefit for hypothermic therapy whereas Georgiou et al. 2013 did not show any clear evidence for hypothermia in TBI-patients. The latter review includes newer publications and comprises much more patients than Cooper et al (2008) so it has the greater impact. The further RCTs (Lee et al 2010, Harris et al. 2009) focus upon metabolic aspects. In summary, no clear evidence for the benefit of hypothermia in TBI – patients is evident at this moment.

10 MANNITOL/HYPERTONIC SALINE

10.1 COCHRANE-REVIEWS

Author(s)/ Title	Wakai A, McCabe A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD001049. DOI: 10.1002/14651858.CD001049.pub5.		
Study types included	Controlled trials in which subjects were assigned to treatment or control groups (placebo-controlled, no drug, different drug or different mannitol regimen) on the basis of random or quasi-random allocation.	**Search period/ databases**	The Cochrane InjuriesGroup Trials SearchCo-ordinator searched the following: 1. Cochrane Injuries Group Specialised Register (20th April 2009); 2. CENTRAL (The Cochrane Library 2009, Issue 2); 3. MEDLINE (OvidSP) (1950 to April 2009); 4. EMBASE (OvidSP) (1980 to April 2009); 5. ISIWeb of Science: Science Citation Index Expanded (SCIEXPANDED) 1970 to April 2009; 6. Conference Proceedings Citation Index- Science (CPCI-S) 1990 to April 2009; 7. PubMed (added in last 6 months; searched 21 April 2009). The reference lists of all relevant articles identified were checked. A letter was sent to the first author of reports to ask for further information on the published report and asking them to assist in identifying any further trials which may have been conducted by them, or other investigators. Eligibility was determined by reading the reports of possible trials.
search algorithm:	The search was limited by date, language or publication type. Search strategies are listed in Appendix 1.		
Inclusion criteria	Controlled trials in which subjects were assigned to treatment or control groups (placebo-controlled, no drug, different drug or different mannitol regimen) on the basis of random or quasi-random allocation. Participants had a clinically defined acute traumatic brain injury of any severity.	**exclusion criteria**	We excluded trials with a cross-over design.

Intervention(s)	The treatment group received mannitol in any dose for any duration, at any time within eight weeks following injury.	**control**	The control group received any of the following: mannitol in a different dose from the treatment group, another ICP-lowering agent such as barbiturates or placebo or standard care only.
Primary Outcome:	We aimed to extract from each trial the number of patients originally allocated to each group. Within each group, we aimed to extract the number of participants who died from any cause during the follow-up period or who were dead, in a vegetative state or severely disabled, compared to moderate or good recovery (according to Glasgow Coma Scale [GCS] criteria).	**Secondary Outcome:**	not reported
Selection of Studies			
Methods (metaanalysis)	We determined eligibility by reading the reports of possible trials and corresponding with the trialists. The reviewers independently rated quality of allocation concealment and independently extracted the data. We resolved disagreement by discussion. We calculated relative risks and 95%confidence intervals for each trial on an intention to treat basis. For trials which used comparable treatment regimens, we planned to calculate summary relative risks and 95% confidence intervals using a fixed effects model, and to stratify the analyses on allocation concealment. No metaaanalysis was done as each study included has a different intervention-control design.	**Allocation**	see Methods
Blinding	see Methods	**Intention-to-treat**	see Methods
drop-out	not reported	**Selective reporting**	see Methods
Main results	• We identified four eligible randomised controlled trials. • One trial compared ICP-directed therapy to 'standard care' (RR for death = 0.83; 95% CI 0.47 to 1.46). • One trial compared mannitol to pentobarbital (RR for death = 0.85; 95% CI 0.52 to 1.38). • One trial compared mannitol to hypertonic saline (RR for death = 1.25; 95% CI 0.47 to 3.33). • One trial tested the effectiveness of pre-hospital , administration of mannitol against placebo (RR for death = 1.75; 95% CI 0.48 to 6.38).		
Conclu	Mannitol therapy for raised ICP may have a beneficial effect on mortality when compared to pentobarbital treatment, but may have a detrimental effect on mortality when compared to hypertonic saline. ICP-		

clusions	directed treatment shows a small beneficial effect compared to treatment directed by neurological signs and physiological indicators. There are insufficient data on the effectiveness of pre-hospital administration of mannitol		
LoE	**1b**	**Reasons for downgrading/ exclusion**	(downgraded since the individual results are based only on one trial each)

10.2 SYSTEMATIC REVIEWS

Not found

10.3 RCTs

Author(s)/ Title	Cottenceau V, Masson F, Mahamid E, Petit L, Shik V, Sztark F, Zaaroor M, Soustiel JF. Comparison of effects of equiosmolar doses of mannitol and hypertonic saline on cerebral blood flow and metabolism in traumatic brain injury. J Neurotrauma. 2011 Oct;28(10):2003-12. doi: 10.1089/neu.2011.1929. Epub 2011 Sep 23. PubMed PMID: 21787184.		
Study type	randomized controlled trial		
Intervention(s)	Whenever appropriate (ICP > 15 mmHG), patients received equiosmolar infusions of hypertonic saline (HTS) 7.5% (2mL/kg;), delivered intravenously within 20 min.	**control**	Whenever appropriate (ICP > 15 mmHG),, patients received equiosmolar infusions of MTL 20% (4mL/kg;), delivered intravenously within 20 min.
a priori subgroups	TBI lesions were categorized into two subgroups: • diffuse (n=21) and • focal brain injuries (n = 26)		
Inclusion criteria	• TBI severe enough to justify ICP monitoring and mechanical ventilation under sedation, • with a Glasgow Coma Scale (GCS) score of $\leq$8 at the time of admission.	**exclusion criteria**	• age < 16 years, • previous history of cerebral vascular disease, • bilateral fixed dilated pupils on admission, • and hypovolemic shock.
Patients for Intervention(s)	n=22 patients	**Patients for control**	n=25 patients
Cross over/	Not reported	**recruiting pe-**	Not reported

protocol violations		**riod**	
Primary Outcome:	before, 30 and 120 min following each infusion • Serum sodium, • hematocrit, • ICP, • arterial blood pressure, • cerebral perfusion pressure (CPP), • shear rate, • global indices of cerebral blood flow (CBF) and metabolism were measured at 6 months: • Neurological Outcome using the Glasgow Outcome Score(GOS) score was assessed	**Secondary Outcome:**	No differentiation between primary and secondary outcome
Power analysis	Not done	**population size**	patients of the HTS group had lower GCS scores on admission that correlated with lower CMR02 values on admission. Rather small population size
randomization process	Before the beginning of the study, 30 opaque envelopes in each hospital had been prepared and numbered sequentially. A computer-generated random-number table was used to assign each consecutive envelope to receive a sheet indicating either MTL or HTL group. Envelopes were then sealed. Randomization was based on blocks of four. The sealed envelopes were opened sequentially throughout the study when a patient fulfilled inclusion criteria	**Intention-to-treat**	Eventually, as no protocol violation reported
follow-up/ drop-out	Obviously no drop-outs	**blinding**	no
flowchart	no	**Adverse**	Not reported

		events/ complications	
Statistics/ confidence intervals	• Partly inadequate. • No CI reported	**CoI/ disclosure**	Author Disclosure Statement: No competing financial interests exist.
Main results primary outcome	Both HTS and MTL effectively and equally reduced ICP levels with subsequent elevation of CPP and CBF, • although this effect was significantly stronger and of longer duration after HTS and • correlated with improved rheological blood properties induced by HTS. • Further, effect of HTS on ICP appeared to be more robust in patients with diffuse brain injury. In contrast, oxygen and glucose metabolic rates were left equally unaffected by both solutions. Accordingly, there was no significant difference in neurological outcome between the two groups.		
Results secondary outcome	No differentiation between primary and secondary outcome		
Conclusions	In conclusion, MTL was as effective as HTS in decreasing ICP in TBI patients although both solutions failed to improved cerebral metabolism. HTS showed an additional and stronger effect on cerebral perfusion of potential benefit in the presence of cerebral ischemia. Treatment selection should therefore be individually based on sodium level and cerebral hemodynamics.		
LoE	**2b**	**Reasons for downgrading/ exclusion**	Due to methodological weakness

Author(s)/ Title	Bourdeaux CP, Brown JM. Randomized controlled trial comparing the effect of 8.4% sodium bicarbonate and 5% sodium chloride on raised intracranial pressure after traumatic brain injury. Neurocrit Care. 2011 Aug;15(1):42-5. doi: 10.1007/s12028-011-9512-0. PubMed PMID: 21298358.		
Study type	Randomized controlled trial		
Intervention(s)	For each episode of intracranial hypertension requiring osmotherapy (unprovoked ICP >20 mmHg for >5 min) patients receive sodium bicarbonate (85 ml 8.4% sodium bicarbonate)	**control**	For each episode of intracranial hypertension requiring osmotherapy (unprovoked ICP >20 mmHg for >5 min) patients receive hypertonic saline (100 ml 5% saline)
a priori sub-	no		

groups			
Inclusion criteria	• TBI requiring sedation, ventilation and ICP monitoring. over 16 years old.	**exclusion criteria**	• if it was anticipated that patients would be extubated or require surgical intervention within 24 h. • Patients with established renal failure (creatinine >150% predicted), or • respiratory disease (history of chronic obstructive pulmonary • Patients were also excluded if they developed acute lung injury (PaO2/FiO2 <200 mmHg).
Patients for Intervention(s)	10 episodes of elevated ICP (in 11 patients) were allocated to the intervention group	**Patients for control**	10 episodes of elevated ICP (in 11 patients) were allocated to the control group
Cross over/ protocol violations	Unclear as one patient may have both treatment arms in consecutive episodes of elevated ICP	**recruiting period**	Between October 2009 and May 2010
Primary Outcome:	The primary outcome measure was change in ICP after treatment	**Secondary Outcome:**	Secondary outcomes included • changes in arterial pH, • sodium, • chloride and • venous osmolality
Power analysis	Not done	**population size**	very small (11 patients)
randomisation process	For each episode of intracranial hypertension requiring osmotherapy (unprovoked ICP >20 mmHg for >5 min) patients were randomised …… The randomisation sequence was determined in blocks of 10 (5:5) and treatment allocations were kept in sealed opaque envelopes.	**Intention-to-treat**	Probably
follow-up/ drop-out	no	**blinding**	Blinding was not possible due to the volume difference.
flowchart	no	**Adverse events/ complications**	Not reported
Statistics/	We used two way ANOVA for repeated measures for ICP comparisons	**Col/ disclo-**	Not reported

confidence intervals	between those episodes treated with intervention or control. We calculated a mean delta ICP (baseline ICP–ICP at 60 min post dosing) and compared this between groups with a t test. No CI were reported	**sure**	
Main results primary outcome	• Analysis of the data using a 2 way ANOVA with epsilon adjusted values of the F-statistic indicates that there was • A statistically significant fall in ICP from baseline at all time points, P < 0.001. • Overall there was no significant difference in ICP with time between those episodes treated with 5% sodium chloride or 8.4% sodium bicarbonate, P = 0.504 • The delta ICP (mean (SD)) at 60 min was 12.1 (4.1) mmHg for bicarbonate and 10.1 (5.1) mmHg for hypertonic saline (difference not significant). • However, after 150 min mean ICP was higher in the hypertonic saline group when compared to the bicarbonate group (P < 0.05, t test).		
Results secondary outcome	• Baseline variables (ICP, serum sodium, serum osmolality, arterial pH, and pCO2) were not different between the treatment groups. • As expected mean pH was significantly increased compared to baseline in the bicarbonate but not the saline group. • There were no significant changes in arterial pCO2, pH, sodium, chloride, or serum osmolality		
Conclu clusions	An equiosmolar infusion of 8.4% sodium bicarbonate is as effective as 5% sodium chloride for reduction of raised ICP after traumatic brain injury when infused over 30 min		
LoE	**2b**	**Reasons for downgrading/ exclusion**	• Methodological weakness • Small sample size • Possible bias as both treatment arms were applied to one patient.

Author(s)/ Title	Bulger EM, May S, Brasel KJ, Schreiber M, Kerby JD, Tisherman SA, Newgard C, Slutsky A, Coimbra R, Emerson S, Minei JP, Bardarson B, Kudenchuk P, Baker A, Christenson J, Idris A, Davis D, Fabian TC, Aufderheide TP, Callaway C, Williams C, Banek J, Vaillancourt C, van Heest R, Sopko G, Hata JS, Hoyt DB; ROC Investigators. Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: a randomized controlled trial. JAMA. 2010 Oct 6;304(13):1455-64. doi: 10.1001/jama.2010.1405. PubMed PMID: 20924011; PubMed Central PMCID: PMC3015143.		
Study type	Multicentre, double-blind, randomized, placebo controlled clinical trial		
Intervention(s)	1. A single 250-mL bolus of 7.5% saline/6% dextran 70 (hypertonic saline/ dextran), 2. 7.5% saline (hypertonic saline),	**control**	3. 0.9% saline (normal saline)
a priori subgroups	A priori secondary analyses included patients with an Abbreviated Injury Score for the head (head AIS) of 4 or greater and 2 or greater, those with documented intracranial hemorrhage, and those requiring emergent craniotomy.		
Inclusion	• blunt mechanism of injury, • age 15 years or older,	**exclusion**	• eligibility for enrolment in the hemorrhagic shock cohort which will be reported in a different publication

criteria	• Glasgow Coma Scale (GCS) score of 8 or less, and • ineligibility for enrolment in the hemorrhagic shock cohort.	**criteria**	• known or suspected pregnancy, • age younger than 15 years, • out-of-hospital cardiopulmonary resuscitation, • administration of more than 2000 mL of crystalloid or any amount of colloid or blood products prior to enrollment, • severe hypothermia (<28°C), • drowning, • asphyxia due to hanging, • burns on more than 20% of total body surface area, • isolated penetrating head injury, • inability to obtain intravenous access, • more than 4 hours between receipt of dispatch call to study intervention, • prisoner status, • and interfacility transfer.
Patients for Intervention(s)	1. n = 373 2. n = 355	**Patients for control**	3. n = 603
Cross over/ protocol violations	1. 14/373 2. 14/355 3. 21/603	**recruiting period**	between May 2006 and May 2009
Primary Outcome:	The primary outcome was 6-month neurologic status based on the Extended Glasgow Outcome Score (GOSE).	**Secondary Outcome:**	Additional assessment of neurologic outcome included • the GOSE at discharge • and 1 month following discharge, • and the Disability Rating Score (DRS) at discharge, • 1 month following discharge, • and 6 months following injury. Other secondary outcomes included • 28-day survival, • survival to hospital discharge, • ICP, • interventions required to manage intracranial hypertension, • fluid and blood requirements in the first 24 hours, • physiologic parameters of organ

			dysfunction, • 28-day acute respiratory distress syndrome–free survival, • Multiple Organ Dysfunction Score, • and nosocomial infections.
Power analysis	A 49% incidence of poor outcome was estimated, and hypertonic fluids were assumed to offer a 15% relative reduction (absolute reduction, 7.5%) in the risk of poor outcome..…. Therefore, we estimated a sample size of 2122 patients to provide an overall power of 80% (1-sided study-wide α=.025, 62.6% power for each of the 2 comparisons) for an attenuated absolute reduction of 6.75% (based on the 10% contamination with truly uninjured patients) for each individual agent vs control, accounting for the primary analysis and 2 interim analyses	**population size**	There were no significant differences in baseline characteristics, injury severity scores, and out-of-hospital care provided between treatment groups
randomisation process	The randomization scheme was 1:1:1.4 for • hypertonic saline, • hypertonic saline/dextran, • and normal saline, respectively. This ratio was chosen because it can be shown that this is technically the most efficient ratio for this setting.23 Patients were individually randomized by administration of a blinded bag of study fluid.	**Intention-to-treat**	The primary analysis was designed as modified intent-to-treat, with all patients who had fluid connected to the intravenous tubing included regardless of how much fluid was administered.
follow-up/ drop-out	6 months 15% compensated by multiple imputations	**blinding**	double-blinded
flowchart	yes	**Adverse events/ complications**	reported as having no differences between the three arms
Statistics/ confidence intervals	Initial analyses of the data indicated the absence of 6-month neurologic outcome data for 15% of the study cohort. Therefore, in addition to the completer analysis, we performed an analysis using multiple hot deck imputations (20 imputations) to estimate the 6-month neurologic outcome. Significance was defined as P<.05 based on 2-sided tests. Differences in means or proportions with 95% confidence intervals are also presented.	**CoI/ disclosure**	None reported.

Main results primary outcome	There was no difference in 6-month neurologic outcome among groups with regard to proportions of patients with severe TBI (GOSE ≤4) (hypertonic saline/dextran vs normal saline: 53.7% vs 51.5%; difference, 2.2% [95% CI, −4.5% to 9.0%]; hypertonic saline vs normal saline: 54.3% vs 51.5%; difference, 2.9% [95% CI, −4.0% to 9.7%]; P=.67).		
Results secondary outcome	There were no statistically significant differences in distribution of GOSE category or Disability Rating Score by treatment group. Survival at 28 days was 74.3% with hypertonic saline/dextran,75.7% with hypertonic saline, and 75.1% with normal saline (P=.88).		
Conclu clusions	Among patients with severe TBI not in hypovolemic shock, initial resuscitation with either hypertonic saline or hypertonic saline/dextran, compared with normal saline, did not result in superior 6-month neurologic outcome or survival.		
LoE	**1b**	**Reasons for downgrading/ exclusion**	

Author(s)/ Title	Baker AJ, Rhind SG, Morrison LJ, Black S, Crnko NT, Shek PN, Rizoli SB. Resuscitation with hypertonic saline-dextran reduces serum biomarker levels and correlates with outcome in severe traumatic brain injury patients. J Neurotrauma. 2009 Aug;26(8):1227-40. doi: 10.1089/neu.2008.0868. PubMed PMID: 19637968		
Study type	Randomized controlled trial		
Intervention(s)	a single 250-mL intravenous infusion of 7.5% hypertonic saline in 6% dextran 70 (HSD)	**control**	250 mL of 0.9% isotonic normal saline (NS).
a priori subgroups	no		
Inclusion criteria	if at any time during pre-hospital care the following were present: • coma or loss of consciousness due to isolated blunt head trauma • and/or a Glasgow Coma Scale (GCS) score of ≤8	**exclusion criteria**	• primary penetrating injury, • previous intravenous therapy ≥ 50ml • a time interval between arrival at scene and intravenous access exceeding 4 h, • age less than 16 years, • were presumed to be pregnant at the scene, • had an amputation or burn, • or had vital signs absent prior to randomization.
Patients for In-	n = 31	**Patients for con-**	n = 33

tervention(s)		**trol**	
Cross over/ protocol violations	none	**recruiting period**	between September 2004 and January 2006
Primary Outcome:	Neurological outcomes at the time of hospital discharge (or at 30 days) or death were assessed in consenting patients using • the Functional Independence Measure (FIM) • the Disability Rating Scale (DRS) • the Glasgow Outcome Scale • (GOS) • and the Glasgow Outcome ScaleExtended (GOSE) • The GOS and the GOSE were also dichotomized into favorable (GOS 4-5, GOSE 5-8) or unfavorable (GOS 1-3, GOSE 1-4) outcomes, • concentrations of SIOOB, NSE, and MBP using commercially available ELISA kits at 12, 24, and 48 h post-resuscitation	**Secondary Outcome:**	no differentiation between primary and secondary outcome
Power analysis	the parent study was not powered to detect differences in the outcome measures, but rather it was a feasibility study	**population size**	The two fluid treatment arms were weil balanced with respect to • age, • GCS, • and other prognostic factors, with no significant differences in presenting symptoms between the HSD and NS groups
randomisation process	Patients, paramedics, physicians, study coordinators, and researchers were all blinded to treatment allocation. Blocks of sequentially numbered, computer randomized, externally identical 250-mL intravenous bags were assigned to each ambulance vehicle. A field logistics research coordinator was responsible for randomization compliance at the vehicle level through daily checks. Compliance at the patient was verified through the randomization number of the product labet and recorded on the data checklist.	**Intention-to-treat**	not reported
follow-up/	no drop-outs	**blinding**	double-blinded

drop-out			
flowchart	no	**Adverse events/ complications**	not reported
Statistics/ confidence intervals	intergroup comparisons between dichotomous variables, including significance in clinical outcomes between the treatment groups, were performed by using Student's t-test for continuous variables, and chi-square test or Fisher's exact test was applied as appropriate for categorical predictor variables. Continuous variables that were not normally distributed were compared using the nonparametric Mann-Whitney U test (mortality). Serial comparisons of biomarker concentrations (time by treatment) were made by two-way analysis of variance (ANOVA) with Tukey-Kramer post-hoc multiple comparisons. Relationships between peak biomarker concentrations and clinical outcome variables were assessed by multiple regression analyses. No CIs were reported	**CoI/ disclosure**	mentioned
Main results primary outcome	Patient survival and functional outcome measures at the time of hospital discharge (if <30 days) or at 30 days do not show statistically significant differences between the two fluid treatment groups. Peak levels of SIOOB (60-fold above control) and NSE (sevenfold above control) were observed in patients resuscitated with NS at admission. Remarkably, by comparison, levels of SIOOB and NSE were up to twofold and threefold lower, respectively, in HSD-treated versus NS-treated patients. Moreover, SIOOB and NSE remained significantly above control values in the NS-resuscitated group for up to 24h, but normalized within 12h in HSD-treated patients.		
Results secondary outcome	no differentiation between primary and secondary outcome		
Conclu clusions	• Pre-hospital resuscitation with HSD is associated with a reduction in serum SIOOB, NSE, and MBP concentrations, which are correlated with better outcome after severe TBI. This authors conclusion, however, is in contrast to their finding that Patient survival and functional outcome measures at the time of hospital discharge or at 30 days does not statistically significant differ between the two fluid treatment groups		
LoE	**4**	**Reasons for downgrad-**	methodological weakness evaluation of doubtful surrogate parameters with Implications that contradict clinical results

		ing/ exclusion	

10.4 SUMMARY

There is still no clear evidence for a benefit in TBI using either mannitol or hypertonic saline solutions in general. From pathophysiological reflections and due to the shown effect of (temporarily) decreasing elevated ICP, the application may be justified in cases of a midbrain syndrome/transtentorial herniation. There seems to be no difference between mannitol and hypertonic saline solutions.

11 INDICATIONS FOR CCT

11.1 COCHRANE-REVIEWS

Not found

11.2 SYSTEMATIC REVIEWS

Author(s)/ Title	Pandor A, Harnan S, Goodacre S, Pickering A, Fitzgerald P, Rees A. Diagnostic accuracy of clinical characteristics for identifying CT abnormality after minor brain injury: a systematic review and meta-analysis. J Neurotrauma. 2012 Mar 20;29(5):707-18. doi: 10.1089/neu.2011.1967. Epub 2011 Oct 26.		
Study types included	Cohort studies of patients with minor brain injury	**Search period/ databases**	Potentially relevant studies were identified through searches of 13 electronic databases including • MEDLINE (1950 to April 2009; supplemented with an update to March 2010), • EMBASE (1980 to April 2009), • CINAHL (1981 to April 2009), • and the Cochrane Library (2009, issue 2). Searches were supplemented by hand searching the reference lists of all relevant studies (including existing systematic reviews) and leading experts in the area of minor brain injury were contacted to identify additional published or other unpublished reports.
search algorithm:	The search strategy used free text and thesaurus terms and combined synonyms relating to the condition (e.g., head injury) with a search filter aimed at restricting results to diagnostic accuracy studies. Language restrictions were not used on any database. Further details on the search strategy can be found in Table S1 (Supplementary Data		
Inclusion criteria	Studies were considered eligible for inclusion if they met the following criteria: • diagnostic cohort study (prospective or retrospective) of adults and/or children (of any age; minimum 20 subjects) with minor brain injury (defined as blunt head injury with a GCS of 13 to 15 at presentation; • studies describing any individual clinical characteristics to identify patients at risk of any intracranial injury or need for neurosurgical intervention, and included a proportion of the cohort undergoing imaging; and	**exclusion criteria**	Full-text non-English language citations were excluded from this review because of limited resources for translation.

	• provided data that allowed true positive (TP), true negative (TN), false positive (FP) and false negative (FN) numbers to be extracted or calculated. • Studies that recruited patients with a broad range of brain injury severities were only included if > 50% of the patients had minor brain injury.		
Intervention(s)	Test Although all clinical variables were considered, we selected 32 clinical characteristics (Tables 1–5) for data extraction on the basis of having reasonably consistent definitions and being relevant to routine clinical practice.	**control**	the reference standard was defined as CT or MRI within 24 h of admission
Primary Outcome:	intracranial injury neurosurgical interventions	**Secondary Outcome:**	
Selection of Studies	Four reviewers (APa, APi, SG, and SH) independently assessed the inclusion of potentially relevant articles in three phases. In phase I, two authors (APa and SH) screened all titles to exclude obviously irrelevant articles (i.e., nonhuman, unrelated to minor brain injury). In phase II, the list of included abstracts that were identified as possibly relevant by title were divided equally between two pairs of authors (APa and APi, SG and SH) and assessed independently by each reviewer for inclusion. The full manuscript of all potentially eligible articles that were considered relevant by either pair of authors was obtained, where possible. In phase III, all relevant full text articles were independently assessed for inclusion (APa and SH, checked by APi and SG) and any disagreements in the selection process (within or between pairs) were resolved through discussion and included by consensus between the four reviewers.		
Methods (metaanalysis)	Data relating to study design, quality, and results were extracted by one reviewer (SH) into a standardized data extraction form and independently checked for accuracy by a second (APa). Any discrepancies were resolved through discussion to achieve agreement. Where differences were unresolved, a third reviewer's opinion was sought (SG or APi). Although all clinical variables were considered, we selected 32 clinical characteristics (Tables 1–5) for data extraction on the basis of having reasonably consistent definitions and being relevant to routine clinical practice. Indices of test performance were extracted or derived from data presented in each primary study of each test. Two-by two contingency tables of TP cases, FN cases, FP cases, and	**Allocation**	The methodological quality of each included study was assessed using a modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. Generally, three studies performed well, receiving a positive assessment of at least 8 (FIG. 2). Potential sources of bias most frequently identified concerned the selection of valid and representative study populations (65 studies included patients who were selectively chosen by being symptomatic at presentation, item 1) and adequate descriptions of the reference standard (item 7). The majority of publications poorly described the following aspects: blinding of both the results of the reference standard and the results of the index test (items 8 and 9), uninterpretable or indeterminate test results (item 11), use of an appropriate reference standard

	TN cases were constructed. Data from cohorts of children were analyzed separately. Data from cohorts of adults, mixed cohorts, and cohorts with no clear description of the age range included were analyzed together. • Pooled estimates based on the following: • data from one study only - observed data; • data from two studies - a fixed effects meta-analysis conducted using the method of DerSimonian and Laird (1986); • data from three or more studies - a full Bayesian meta-analysis conducted using the bivariate random effects method of Reitsma et al. (2005). results also included estimated heterogeneity (Q) statistics and corresponding p-values for sensitivity and specificity, calculated using a fixed-effects approach.		(item 3a), and the availability of clinical information (item 10).
Blinding	see allocation	**Intention-to-treat**	not applicable
drop-out	see allocation	**Selective reporting**	see allocation
Main results	• Data were extracted from 71 studies (with cohort sizes ranging from 39 to 31,694 patients) • Depressed or basal skull fracture were the most useful clinical characteristics for the prediction of intracranial injury in both adults and children (positive likelihood ratio [PLR], > 10). • Other useful characteristics included focal neurological deficit, post-traumatic seizure (PLR > 5), persistent vomiting, and coagulopathy (PLR 2 to 5). • Characteristics that had limited diagnostic value included loss of consciousness and headache in adults and scalp hematoma and scalp laceration in children. • Other characteristics, such as headache in adults and scalp laceration of hematoma in children, do not reliably indicate increased risk.		
Conclu clusions	See results. This meta-analysis has a significant risk of bias due to the large amount of heterogeneity was found between the studies. This may be due to the prevalence of intracranial injury, which varied widely between studies and is likely to be caused by differences in the inclusion criteria, adequacy of reference standards, and definitions of intracranial injury.		
LoE	**2a**	**Reasons for downgrading/ exclusion**	Large heterogeneity between studies. Significant amount of retrospective cohort studies or unclear design.

Author(s)/ Title	Undén J, Romner B. Can low serum levels of S100B predict normal CT findings after minor head injury in adults?: an evidence-based review and meta-analysis. J Head Trauma Rehabil. 2010 Jul-Aug;25(4):228-40. doi: 10.1097/HTR.0b013e3181e57e22		
Study types included	Mainly exploratory prospective cohort studies, one with validation of predetermined cutoff level	**Search period/ databases**	between 1983 and 2010(?)
search algorithm:	Medline: combinations of MeSH terms and key words: head injury, TBI, mTBI, MHI, minor, mild, minimal, serum, biomarkers, S-100, S100, S-100B, S100B, S-100BB, S100BB, computed tomography, CT, CCT, and Management A less comprehensive TripDataBase and Clinical Queries search using these key words was also conducted.		
Inclusion criteria	Studies containing adult patients with nonpenetrating head injury with an admission/ initial GCS score of 13 or more, S-100B levels in serum and cranial CT within 24 hours of injury and possibilities for extraction of relevant data (sensitivities, specificities, positive predictive values [PPV], negative predictive values [NPV], and prevalence) for the relevant patient group were included.	**exclusion criteria**	Studies concerning children were excluded.
Intervention(s)	**Index test** The analysis of S1OOB in serum has been achieved through several different techniques, including immunoradiometric assays, immunoluminometric assays, enzyme-linked immunosorbent assays, and lectrochemiluminescence immunoassays. These are available from several commercial sources and differ in performance. For the purpose of simplicity in this report, no distinction will be made between different assays despite the fact that discrepancies in analytical performance may be of importance. The included studies use different assays for detection of S 1OOB in serum, which is a potential source of error	**control**	**Reference test** CT is not very sensitive for intracranial complications after MHI. However, cranial CT is widely accepted as the gold standard in detection of intracranial lesions after MHI and evidence shows that patients with a normal CT scan after MHI have a minimal risk of developing an intracranial lesion. Cranial CT will therefore be considered as the reference test in this report.
Primary Outcome:	not clearly defined intracranial lesion in CT (reference test)	**Secondary Outcome:**	
Selection of Studies	The eligible studies were examined and relevant data recorded including; first author, year of publication, study design, patient group and inclusion criteria, characteristics of the index test including cutoff used, relevant results with respect to the key question including predictive statistics, and study limitations. If certain key factors or data were missing from the studies, authors were contacted for clarification. In the case of multiple studies from the same research group, authors were also contacted to ensure		

	unique patients. Because a cutoff of 0.10 µg/l has independently been reported from different research groups, results in relation to this level were extracted, if possible, to attempt an interpretation of data using the same cutoff.		
Methods (metaanalysis)	Studies are briefly presented in evidentiary tables. Data are presented in table form with corresponding number of patients with true positives (TPs), false positives (FPs), false negatives (FNs), and true negatives (TNs) for each study along with relevant comments concerning FN patients. We explored heterogeneity using a using a Chi-squared test. Because of heterogeneity, weighted pooled sensitivity and specificity were calculated with a random effects model. We calculated likelihood ratios and predictive values from the pooled sensitivities and specificities derived from the random effects model.	**Allocation**	most studies are prospective, however no information concerning allocation is reported
Blinding	no information	**Intention-to-treat**	not applicable
drop-out	no information	**Selective reporting**	Most studies have a high risk of selection bias
Main results	Sensitivities were only borderline homogenous (Q = 19, degrees of freedom = 11, P = 0.054) but specificities were clearly heterogeneous (Q= 168, P < .001). Considering only those studies in which a cutoff of 0.10 µg/L could be evaluated did not eliminate heterogeneity (Q = 15, degrees offreedom 7, P= .042 for sensitivity and Q = 27, degrees of freedom 7, P < .001 for specificity). The pooled sensitivity for all studies was 97% (95%-CI 91 %-99%) and the pooled specificity 40% (95%-CI 30%-51 %). Considering the 6 studies where a cutoff of 0.10 µg/L could be evaluated, sensitivities and specificities were 96% (95%-CI 85%-99%) and 30% (95%-CI 23%-38%), respectively. The prevalence of intracranial findings after MHI has been reported to be in the ranges of 1 % to 10%. Corresponding NPVs for prevalence levels of 1 %, 5%, 10%, and 20% are 100% (95%-CI 100%-100%), 100% (95%-CI 99%-100%), 99%(95%-CI 97%-100%), and 98%(95%-CI 94%-99%), respectively. PPVs considering prevalence levels of 1 %, 5%, 10%, and 20% are 2% (95%-CI 1 %-2%), 8% (95%-CI 7%-9%), 15%(95%-CI 13%-18%), and 29% (95%-CI 25%-33%), respectively. The average prevalence from the included studies in this article was 8%, giving a NPV of more than 99% (95%-CI 98%- l 00%).		
Conclu clusions	Low serum S-100B levels accurately predict normal CT-findings after MHI in adults. The evidence in this report supports a grade B recommendation. S-100B sampling should be considered in MHI patients with no focal neurological deficit, an absence of significant extracerebral injury, should be taken within 3 hours of injury and the cutoff for omitting CT set at less than 0.10 µg/l. Approximately one third of CT scans may be omitted using this approach in the defined patient group, although care givers should be aware of other clinical factors predictive of intracranial complications , after MHI.		

LoE	**2a**	**Reasons for downgrading/ exclusion**	Due to the dominating type of included studies The included studies use different assays for detection of S 1OOB in serum, which is a potential source of error Most studies have a high risk of selection bias

11.3 RCTs

Author(s)/ Title	Ding J, Yuan F, Guo Y, Chen SW, Gao WW, Wang G, Cao HL, Ju SM, Chen H, Zhang PQ, Tian HL. A prospective clinical study of routine repeat computed tomography (CT) after traumatic brain injury (TBI). Brain Inj. 2012;26(10):1211-6. doi: 10.3109/02699052.2012.667591. Epub 2012 May 9. PubMed PMID: 22571813.		
Study type	Randomized controlled trial		
Intervention(s)	the routine CT-scanning group: Computerized tomography (CT) scans of patients in the first group were routinely obtained on admission and thereafter. In the first group, CT was performed at 6-8 hours, 20-24 hours, 48 hours and 7 days after injury. When the condition of patients changed, immediate CT scanning was performed.	**control**	the non-routine CT-scanning group: In the second group, CT scanning was performed only when the conditions of patients changed. Condition change was categorized as change of level of consciousness, pupillary change, motor examination change, increased ICP or loss of brainstem reflexes.
a priori subgroups	no		
Inclusion criteria	patients who suffered TBI without subsequent surgery	**exclusion criteria**	To prevent interference from confounding variables, • patients who were immediately treated with a craniotomy, • died within 3 days, • experienced severe multiple injuries or • failed to undergo repeat CT scanning for any reason were excluded from the study.
Patients for Intervention(s)	n = 89	**Patients for control**	n = 82
Cross over/ protocol violations	Not reported	**recruiting period**	1 January 2009 to 30 June 2010.

Primary Outcome:	• Length of stay on ICU (ICU-LOS) • and in hospital (LOS) • Charges • GCS at discharge	**Secondary Outcome:**	No differentiation between primary and secondary outcome
Power analysis	Not done	**population size**	Sample size not based upon a power analysis The two groups did not differ significantly in terms of age, sex or GCSO ($p > 0.05$).
randomization process	Allocation was done using a random number table.	**Intention-to-treat**	Obviously, but not explicitly mentioned.
follow-up/ drop-out	No drop-outs	**blinding**	no
flowchart	no	**Adverse events/ complications**	Not described
Statistics/ confidence intervals	T-tests were used to compare the results of the two groups. Measurement data were presented as mean ± SD. All variables were included as candidates in a stepwise logistic regression model to assess independent associations with progressive brain injuries….. Variables with p-values of < 0.05 were considered statistically significant. No CI were indicated.	**CoI/ disclosure**	The authors report no conflicts of interest.
Main results primary outcome	The death of five patients in each group is reported, however, without the interval after randomization. According to the text they were excluded from the evaluation of the GCS-score at discharge. It remains unclear, how the authors handled that fact concerning the other outcome parameters. A bias cannot be excluded. The results revealed statistically significant differences between the two groups in terms of neuro-ICU-LOS and LOS ($p < 0.01$). No significant differences emerged with respect to hospital charges and GCS scores at discharge ($p > 0.05$). Age, international normalized ratio (INR), D-dimer concentration (DD), GCS scores and number of hours between the first CT scan and the injury (HCTI) were influential factors of developing progressive haemorrhage.		
Results secondary outcome	No differentiation between primary and secondary outcome		

Conclu clu-sions	The routine-repeat CT group fared better than did the non-routine-repeat CT group. However, the only statistically significant result is the shortening of ICU-LOS and LOS, if routinely repeated CT-scans were done and this result may be affected by bias (s. above). Routinely repeated CTs were minimally effective among those with mild TBI, whereas this procedure demonstrated a significant effect on patients with moderate and severe TBI. There is no a priori sub-group definition suited to support this hypothesis		
LoE	**4**	**Rea-sons for down-grad-ing/ ex-clusion**	Methodological weakness, Possible bias

11.4 SUMMARY

The review by Pandor et al (2012) confirmed known factors predicting developing brain injury e.g. intracranial bleeding in mild TBI. The systematic review by Under and Romnen (2010) implicate that in mild head injury S100B serum levels may trigger or omit a CCT-scan. The pooled negative predictive value of 99% seems to be rather convincing. However, mainly studies with a 2b level of evidence were included. The paper by Ding et al (2012) again emphasizes the value of routinely repeated CT-scans, however, the methodological quality is very weak.