Clinical Practice Guideline

Diagnosis and treatment of adult patients with severe Traumatic Brain Injury

General System of Social Security in Health–Colombia


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Introduction

Traumatic brain injury (TBI) is defined as an condition characterized by a brain disorder secondary to a traumatic injury produced by the liberation of an external force, be it in the form of mechanical, chemical, thermal, electrical, radiant energy, or any combination thereof. This transmission of energy to the cranial cavity causes structural damage to its content, including brain tissue and the blood vessels that feed this tissue (Rubiano 2009). The TBI can be classified in many ways, including whether it is penetrating or closed and depending on the anatomical area that is affected. According to the consensus of guidelines for the unification of variables in studies of neurotrauma, the Glasgow Coma Scale is one of the most appropriate scales for associating the clinical presentation with the outcomes, taking into account that this classification was one of the first that allowed the association of findings with clinical evaluation, imaging and post mortem macroscopic pathology (Saatman 2008). This is the most widely used classification in national and international environments, and selects patients according to the degree of severity. This scale has been developed based on the clinical evaluation of 3 parameters: eye opening, verbal response and motor response (see table 1).
### TABLE 1. Glasgow Coma Scale

<table>
<thead>
<tr>
<th>EYE RESPONSE OR EYE OPENING</th>
<th>VERBAL RESPONSE</th>
<th>MOTOR RESPONSE</th>
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<tbody>
<tr>
<td>Do not open (1)</td>
<td>No verbal response (1)</td>
<td>No motor response (1)</td>
</tr>
<tr>
<td>Upon pain stimulus (2)</td>
<td>Incomprehensible sounds or guttural speech (2)</td>
<td>Abnormal extension response or descerebration (2)</td>
</tr>
<tr>
<td>Upon speech stimulus (3)</td>
<td>Words out of context (inappropriate response) (3)</td>
<td>Abnormal flexion response or decortication (3)</td>
</tr>
<tr>
<td>Spontaneous (4)</td>
<td>Disoriented in some of the 3 spheres (confused) (4)</td>
<td>Withdraws from nociceptive or painful stimuli (4)</td>
</tr>
<tr>
<td></td>
<td>Oriented in the 3 spheres (5)</td>
<td>Localizes nociceptive or painful stimuli (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obeys orders or makes spontaneous movements (6)</td>
</tr>
</tbody>
</table>

The Glasgow Coma Scale allows the association of the clinical situation of the patient with the severity of the injury. The score must be measured after initial resuscitation. These definitions correlate with a probability of clinical deterioration that will cause a surgical outcome or mortality.

The first parameter (eye opening), correlates the degree of required stimulus to carry out this action, with a score of 1 given to patients who are unable to open their eyes with a nociceptive (painful) stimuli. 2 points are given to patients who open their eyes to nociceptive stimuli; 3 to patients who open the eyes to auditive stimuli; and 4 points are given to patients who open their eyes spontaneously. For the evaluation of verbal response, a score of 1 signifies that the patient is not able to make sounds following nociceptive stimulus; 2 means that the patient makes incomprehensible sounds; 3 is for a patient who responds in an incoherent way; 4 for a patient who responds showing disorientation;
and 5 indicates that the patient responds appropriately to questions from the examiner. The motor activity is the last parameter (which is considered one of the most important as it is not affected by the use of sedative or toxic medications). A score of 1 is assigned to patients that do not make any sort of movement following nociceptive stimuli; 2 is given to patients that respond with an abnormal extension movement (decerebration); 3 points are for patients who respond with an abnormal flexion movement (decortication); A score of 4 is given to patients who make withdrawal movements to stimuli; patients who can localize the stimulus receive a score of 5; and 6 for patients who make movements that are spontaneous or when induced to obey a verbal order. Therefore, adding up the scores for the 3 parameters, we can create categories:

- Mild TBI (Glasgow 13-15)
- Moderate TBI (Glasgow 9-12)
- Severe TBI (Glasgow 3-8)

These categories have been correlated to mortality, disability and the requirement for surgical intervention, all of which are greater in the severe TBI group.

Additionally, a second severity classification method has been suggested specifically to compare the medical records of patients treated in specialized centers. Comparing these medical records allows us to establish differences in patients with multiple types of injury and to establish methods and mathematical models in order to determine survival rates. The most used score is the Abbreviated Injury Scale. This system has a range of 1 to 5, where 1 is for superficial and less complex injuries and 5 is for the most severe injuries (see table 2). It is considered that all head injuries with scores greater than 2 are severe and are associated with greater mortality and disability.
**TABLE 2. Abbreviated Injury Scale (AIS) for head injuries, closed and penetrating**

**ABBREVIATED INJURY SCALE (AIS) FOR CLOSED TRAUMA**

<table>
<thead>
<tr>
<th>A.I.S. SCALE</th>
<th>1 LOW</th>
<th>2 MODERATE</th>
<th>3 SERIOUS</th>
<th>4 SEVERE</th>
<th>5 CRITICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEAD</td>
<td>Cephalea or vertigo secondary to TBI.</td>
<td>Amnesia of the accident. Lethargic/stuporous or wakes up through verbal stimulus. Unconsciousness for less than an hour. Simple fracture of the cranial cavity.</td>
<td>Unconscious for 1-6 hours. Unconscious for &lt;1 hour with neurological deficit. Fx skull base. Cerebral contusion / subarachnoidal hemorrhage.</td>
<td>Unconscious for 1-6 hours with neurological deficit. Unconscious for 6-24 hours. Appropriate response to painful stimulus only. Fx of the cranial cavity with a depression of &gt;2cm. Rupture of the dura mater. Intracranial hematoma of 100c.c.</td>
<td>Unconsciousness with inappropriate movements. Unconsciousness for &gt;24 hours. Injury of brain stem. Intracranial hematoma &gt;100c.c</td>
</tr>
</tbody>
</table>

**ABBREVIATED INJURY SCALE (AIS) FOR PENETRATING TRAUMA**

<table>
<thead>
<tr>
<th>A.I.S. SCALE</th>
<th>1 LOW</th>
<th>2 MODERATE</th>
<th>3 SERIOUS</th>
<th>4 SEVERE</th>
<th>5 CRITICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEAD</td>
<td>Complex penetrating cervical trauma with little tissue loss and without organic injury. Minor laceration of the carotid or vertebral artery or the internal jugular vein. Small transection of the jugular vein.</td>
<td>Serious laceration of the carotid and/or vertebral artery. (positive neurological signs). Transection of the carotid or vertebral artery.</td>
<td>Penetrating cranial trauma with entry and exit wounds. Penetrating trauma of the brain or cerebellum. Segmentary loss of the carotid or vertebral artery.</td>
<td></td>
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The abbreviated injury scale (AIS) allows the establishment of prognostic correlations according to the severity of the injury. This contains clinically evaluable criteria on the patient at the time of admittance to emergency departments or during intrahospital treatment, including imaging or intra-operative findings.
From the epidemiological point of view, TBI is one of the most important medical-surgical conditions at a global level. In the world, there are incidence estimates of near to 200 cases for every 100,000 inhabitants, but the limited availability of epidemiological databases, especially in countries with medium and low incomes (in which around 90% of the population with TBI are concentrated), means that these estimates are not very precise. It is clear, according to recent studies, such as the global burden of disease study performed by the WHO, that in areas such as Latin America, the impact of this condition is relatively high, with trauma in general being the most common cause of death and disability in the population between 10 and 24 years (Norton 2012). In Colombia, the data available, until 2008, allows the identification of trauma as the principal cause of death and disability in 12 to 45 year olds (WHO 2010). According to data from the National Institute of Legal Medicine and Forensic Sciences, for the year 2012, multiple trauma (including TBI) corresponded to 65.5% of the fatal injuries in traffic accidents, followed by isolated TBI with 27.2% (Moreno 2012). Due to the above, it is clear that TBI as a condition is a public health problem and that it is vital to develop clinical practice guidelines in order to reduce variability in the treatment, oriented to the performing of an integral care of patients with the best scientific evidence and strengthened public policy towards a high quality health care.

**Background**

The Colombian Ministry of Health has made an important effort in the development of clinical practice and care guidelines since the 1990s. During that first exercise, in a joint project with ASCOFAME, the Ministry of Health and the Social Security Institute, the topic of TBI was identified as a priority, due to its high incidence in the population of Colombia. During the development of the second edition of the national emergency care guidelines (MPS 2004) and the first edition of the prehospital medical care guidelines (MPS 2005), TBI was also considered a priority topic, and specific chapters of reviews of the management of this condition were included. These care guides currently have revised and updated chapters on the topic in the latest edition of each one (MPS 2009) (MPS 2012). In the new phase of the creation of clinical practice guidelines, TBI continues to be a priority topic, recognizing its impact in the scenario of Colombian public health and due to
this issue, it was made part of funding announcement 563-12, product of a joint effort between the Ministry of Health and Colciencias.

**Rationale**

The availability of a CPG for the diagnosis and treatment of severe TBI in adults implies a reduction in the variability of treatment and a high quality approach to diagnosis and treatment, based on the best available scientific evidence. Although there are different types of guidelines around the world, the methodological quality of their production has not been the most appropriate according to international standards (Alarcón 2013). Additionally, the great majority of the available guidelines are developed for contexts that are different to most of the countries in Latin America, were not all the technology available for advanced monitoring of patients with severe TBI is available all around. Adherence to the use of recommendations of guidelines with high methodological quality for the treatment of TBI has been linked to improvements in survival rates and cost reduction within healthcare systems (Fakhry 2004) (Faul 2007) (Gerber 2013). Some of the most critical interventions are those that present greater variability in different scenarios, including the prehospital care phase and intrahospital treatment in terms of emergencies, surgery and intensive care. Therefore, the production of a CPG for the diagnosis and treatment of patients with severe TBI in Colombia is considered necessary, because in the country, this condition add an important burden of disease in the health system and additionally the care is heterogeneous due to the inexistence of this type of tools. Currently there is evidence available that allows the creation of recommendations based on a systematic and technically aseptic process. A preliminary review of the literature suggests that interventions such as early intubation in the prehospital phase, early surgical intervention, the use of specific neuromonitoring protocols at intensive care and the use of medications that can reduce the impact of secondary injuries, have been associated with a reduction in mortality and disability.

**Conflict of interest declaration**

The activities that may constitute conflicts of interest are those circumstances in which professional judgment on a primary interest, such as
the safety of patients or validity of research can be affected by another secondary interest, which could be a financial benefit, prestige, personal or professional promotion. An interest is considered specific if it is directly related to technologies or products being evaluated in a CPG. An unspecific interest is one that is not related directly to technologies or products being evaluated in the CPG, but which may be related indirectly due to interactions with the manufacturer, marketer, users, etc., of these products. Conflict of interest declarations of each one of the members of the developer group can be found in annex 1 of the complete version of this guide.

Financing of the CPG

The development of this guide was funded by the Ministry of Health and Social Protection and the Administrative Department of Science, Technology and Innovation (COLCIENCIAS) through contract No. 455 of 2012 signed with the Foundation for Medical and Technical Education and Research in Emergencies and Disasters (MEDITECH), an institution that was selected through the funding announcement 563 of 2012 for the developing of Clinical Practice Guidelines for the Diagnosis, Treatment and Rehabilitation of Patients with Traumatic Brain Injury.

Editorial Independence

The scientific work of research and production of the recommendations included in this document was made independently by the guide’s developer group. Funding institutions monitored the production of this document in order to guarantee the unconditional freedom of the contents of the guide.

Scope of the topic of the CPG

This CPG for the diagnosis and treatment of patients is designed for the adult population with severe Traumatic Brain Injury (TBI) in Colombia, considering as adults all persons over 15 years old, according to international standards for research into severe TBI; The recommendations are also directed at prehospital healthcare personnel, general physicians, paramedics, emergency surgeons, neurologists, neurosurgeons, intensive care doctors, patients and caregivers of patients.
**Objectives of the CPG**

The objective of the CPG for the diagnosis and treatment of adult patients with severe TBI is to reduce the heterogeneity in the diagnosis and treatment of this kind of patients in Colombia, with the aim of improving the quality of care, reducing disabilities and increasing the survival rate for these patients.

**Specific objectives**

- To reduce the heterogeneity of prehospital and intrahospital care for severe TBI in Colombia in order to encourage evidence-based practice.
- To establish criteria for referral and transfer of adult patients with TBI in a trauma care system.
- To promote efficient use of scans of the skull to focus the diagnosis and treatment of TBI in adults.
- To establish criteria for the appropriate use of intravenous fluids and management of the airway at prehospital and intrahospital levels in adult patients with severe TBI, reducing the heterogeneity in treatment and with the aim of improving functional outcome.
- To establish criteria associated with the most appropriate time to carry out surgical procedures in adult patients with severe TBI, with the aim of improving the functional outcome of these patients.
- To establish criteria for the use of sedatives in the treatment of adult patients with severe TBI in intensive care units, reducing heterogeneity in their use.
- To decrease heterogeneity in the treatment of thromboprophylaxis, monitoring of intracranial pressure and treatment with selective hypothermia in adult patients with severe TBI treated in intensive care units, with the aim of improving functional outcome in these patients.
- To define the cost-effectiveness of the treatment with prehospital intubation of adult patients with severe TBI compared with intra-hospital intubation.
Users

Prehospital healthcare personnel, nurses, general practitioners, specialists in emergency medicine, emergency surgeons, neurologists, neurosurgeons, intensive care doctors, patients, caregivers, family members and decision makers.

Population to whom the CPG is directed

The people to whom the CPG for the diagnosis and treatment of severe TBI is directed are persons over 15 years old who have a traumatic brain injury.

Healthcare workers to whom the CPG is directed

Prehospital health care personnel, including nurses, technicians or technologists in prehospital care and general physicians who work in this environment. Nurses and general practitioners from low-complexity level institutions; In medium-complexity level institutions, nurses, general practitioners and medical specialists who assist in emergency services; In high-complexity level institutions, nurses, general practitioners and specialists in emergency medicine, emergency surgeons, neurologists, neurosurgeons and intensive care doctors who provide specialized services in emergency departments, surgery and intensive care.

Clinical aspects covered by the guide

The Guide refers to the diagnosis and interventions used to treat patients over 15 years old with severe TBI. It addresses the following aspects of clinical treatment:
   a) Aspect 1. Prehospital Treatment
   b) Aspect 2. Emergency Treatment
   c) Aspect 3. Treatment in Intensive Care Units

Clinical aspects not covered by the guide

The guide does not cover the following aspects of clinical treatment:
   a) Aspects of prevention and surveillance of injuries
b) Aspects of rehabilitation  
c) Aspects of diagnosis and treatment of patients under 15 years old  
d) Aspects related to alternative therapies  
e) Aspects of therapies in the experimentation phase  

**Updating the CPG**

The recommendations of this guideline must be updated in the next three (3) years or earlier if there is new evidence that modify the recommendations or any of the specific questions. The updating process must follow the previously established methodology and must be coordinated together with the Ministry of Health and the IETS.

**References**

10. Fakhry SM, Trask AL, Waller MA, Watts DD; IRTC Neurotrauma Task Force. Management of brain-injured patients by an evidence-


Summary of recommendations

Question 1a

Which patients with TBI should have a computerized tomography (CT) of the head?

Recommendation

- It is recommended that every adult patient with TBI and who meet one or more of the following criteria must be have a CT scan:
  - Skull fracture (clinical or radiological) including signs of basilar skull fracture (periorbital ecchymosis, retroauricular ecchymosis, otorrhea, rhinorrhea).
  - Post-traumatic seizure
  - Focal neurological deficit
  - Persistent vomiting (greater than or equal to two episodes)
  - Drop in the Glasgow Coma Scale of at least 1 point
  - Previous craniotomy
  - When the patient is a pedestrian who was hit by a car.
  - History of coagulopathy or pharmacologic anticoagulation
  - Patients suspected to be intoxicated.
  - Fall from height greater than 1.5 m
  - Retrograde Amnesia> 30 minutes and/or anterograde
  - Age greater than or equal to 60 years.
  - Severe headache
  - Blurred vision or diplopia
Question 1b

Which patients with TBI should be transferred from low-level of care hospitals to centers with neurosurgery and neuroimaging services?

Recommendation

- It is recommended that patients with moderate to severe TBI (Glasgow 3-12) should be transferred immediately to high-level of care hospitals with access to neuroimaging and neurosurgery.

- It is recommended that patients with mild TBI (Glasgow 13-15) who present one or more of the following criteria be referred for evaluation at an institution that has access to neuroimaging and neurosurgery:
  - Glasgow coma score under 15 up to 2 hours after injury
  - Severe headache
  - More than 2 episodes of vomiting
  - Skull fracture, including depressed fractures or clinical signs of fracture of the skull base (raccoon eyes, retro auricular ecchymosis, otorrhea or rhinorrhea)
  - Age greater than or equal to 60 years old
  - Blurred vision or diplopia
  - Post-traumatic seizure
  - Focal neurological deficit
  - Previous craniotomy.
  - Fall of over 1.5 meters.
  - Retrograde amnesia more than 30 minutes and/or anterograde amnesia.
  - Suspected intoxication with alcohol and/or psychoactive substances.

- It is recommended that patients with mild TBI and who are in active treatment with anticoagulants, have active coagulopathies, or are pregnant should be transferred to centers with neurosurgery and neuroimaging services.
Question 2

In adult patients with severe TBI, does the treatment in an organized trauma care center, compared to treatment in a general non-specialized center reduce mortality?

Recommendation

- It is suggested that adult patients with severe TBI be transferred directly to a leading high-complexity institution with emphasis on trauma care.
  ✓ Weak recommendation in favor of intervention, low quality evidence.

Question 3

In adult patients with severe TBI, does prehospital orotracheal intubation, compared with orotracheal intubation in emergency departments, reduce neurological disability or mortality, evaluated at 6 months post-injury?

Recommendation

- It is recommended that adult patients with severe TBI need to be intubated in the trachea in a prehospital setting, using a rapid sequence intubation, which includes inductor medication and neuromuscular paralysis medication.
  ✓ Strong recommendation in favor of intervention, moderate quality of evidence.
- The recommended dosages to be used are the following:
  - *Fentanyl Dose*: 1 μg/Kg
  - *Midazolam Dose*: 0.1mg/Kg
  - *Succinylcholine Dose*: 1 mg/Kg
  ✓ Strong recommendation in favor of intervention, moderate quality of evidence.
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>The use of half the dose of inductor medications suggested above is recommended if the patient has systolic blood pressure &lt;100mmHg, or is &gt;60 years old.</td>
<td>Strong</td>
</tr>
<tr>
<td>Orotracheal intubation in a prehospital setting should be carried out by skilled medical personnel or prehospital technologists (who have an adequate level of training). Technologists must carry out the procedure under direct or indirect supervision of a doctor with experience in handling prehospital and in-hospital emergencies.</td>
<td>Weak</td>
</tr>
<tr>
<td>We suggest that adequate training as part of intubation training programs should be considered to be at least 16 hours of theoretical-practical training in rapid sequence intubation, including at least 4 hours of theory, 8 hours of experience in intubation in operating theaters under the supervision of an anesthesiologist and at least 4 hours of evaluation in simulators.</td>
<td>Weak</td>
</tr>
<tr>
<td>It is recommended that if the attempt to intubate is not successful, patients should continue to be ventilated with a bag valve mask system, together with an oropharyngeal airway, until they return to spontaneous respiration. If this method is insufficient to achieve a pulse oximetry &gt;90%, we recommend the use of a laryngeal mask, as a rescue device.</td>
<td>Strong</td>
</tr>
<tr>
<td>It is suggested that in the case that the patient is being moved by a basic ambulance, and there is no technologist or medic on board, ventilation should be carried out with a bag valve mask system, together with an oropharyngeal airway in order to achieve a pulse oximetry of &gt;90%.</td>
<td>Good</td>
</tr>
</tbody>
</table>

Strong recommendation, moderate quality of evidence

Weak recommendation in favor of intervention, low quality of evidence

Weak recommendation, moderate quality of evidence

Strong recommendation in favor of intervention, moderate quality of evidence

Good clinical practice
Question 4

In adult patients with severe TBI, does the use of 7.5% hypertonic solutions for resuscitation in prehospital setting, compared with the use of isotonic resuscitation solutions, reduce neurological disability or mortality, evaluated at 6 months post-injury?

Recommendation

- It is recommended that adult patients with severe blunt TBI without hypotension can be treated at a prehospital level with 250ml of saline solution at 0.9%
  ✓ Strong recommendation in favor of intervention, moderate quality of evidence

- It is recommended that patients with penetrating TBI or with hypotension can be treated at a prehospital level with 250ml of saline solution at 0.9%
  ✓ Good clinical practice.

Question 5

In adult patients with severe TBI and intracranial hypertension, does the use of hypertonic saline at 7.5%, compared with mannitol, as a hyperosmolar initial therapy reduce mortality at discharge?

Recommendation

- It is suggested that adult patients with severe TBI and refractory intracranial hypertension (ICP> 25 mmHg for more than 5 minutes, measured with an intracranial pressure measuring device) be treated with a bolus of 2 ml/kg of 7.5% hypertonic saline solution or mannitol at 20%.
  ✓ Weak recommendation in favor of intervention, moderate quality of evidence.
• If the first dose is not effective in reducing ICP, a second bolus of 7.5% hypertonic saline solution or mannitol at 20% may be administered 10 minutes after finishing the first bolus.
✓ Weak recommendation in favor of the intervention, moderate quality of evidence.

• It is considered that adult patients with severe TBI and non-refractory intracranial hypertension (20-25mmHg, measured using an intracranial pressure device) requiring hyperosmolar therapy should be treated with a bolus of 2 cc/kg of 7.5% hypertonic saline solution or mannitol at 20%.
✓ Good clinical practice

• It is considered that for the preparation of the 7.5% hypertonic saline solution, a mixture of (40%) 0.9% saline solution plus (60%) ampoules of sodium chloride should be used. To prepare 250cc of the solution, 100cc of normal saline solution and 15 ampoules of sodium chloride (20meq/10ml) would be mixed.
✓ Good clinical practice

• It is considered that the use of mannitol at 20% should be performed only in normotensive patients with systolic blood pressure greater than 90 mmHg.
✓ Good clinical practice

**Question 6a**

In adult patients with severe TBI and acute subdural hematoma with surgical indication, does early drainage surgery (within 4 hours), compared with late surgery (after 4 hours), reduce mortality at discharge?
Recommendation

- It is recommended that surgical treatment be performed in the first 4 hours post-trauma in patients with severe head trauma with acute subdural hematoma with surgical indication.
  ✓ Recommendation by strong consensus in favor of the intervention.

Question 6b

In adult patients with severe TBI, and an epidural hematoma with surgical indication, does early drainage surgery (within 4 hours), compared with late surgery (after 4 hours), reduce mortality at discharge?

Recommendation

- It is recommended that patients with severe TBI and an epidural hematoma with surgical indication for drainage be taken to surgery immediately.
  ✓ Recommendation by strong consensus in favor of the intervention.

Question 6c

In adult patients with severe TBI and surgical indication for cerebral edema, does early decompression craniectomy (within 24 hours), compared with late craniectomy (after 24 hours), reduce mortality at discharge?

Recommendation

- It is suggested that patients with severe TBI and surgical indication for cerebral edema be taken to surgery within 24 hours.
  ✓ Weak recommendation in favor of the intervention, low quality of evidence.
Question 7

In adult patients with severe TBI being treated in an ICU, does sedation with propofol, compared to sedation using Midazolam, reduce neurological disability or mortality, assessed at 3 months post-injury?

Recommendation

• It is suggested that adult patients with severe TBI be sedated during their stay in the ICU using midazolam. Doses of 0.1-0.3 mg/kg/h are suggested.¹
  ✓ Weak recommendation in favor of the intervention, moderate quality of evidence

• As a second choice after midazolam, propofol 1% can be used at a dose of 1.5 to 5 mg/kg/h¹.
  ✓ Weak recommendation in favor of the intervention, moderate quality of evidence

• It is suggested that a triglyceride measurement be performed on patients sedated with propofol 1% within the first 24 hours. If the initial sample of triglycerides is lower than 350 mg/dl, periodic checks should be performed every 72 hours. If the value is greater than 350 mg/dl, repeat the sample within 24 hours. If the second sample is also above 350 mg/dl, treatment should be discontinued immediately. Patients should be closely monitored for the possible occurrence of propofol infusion syndrome (hyperkalemia, metabolic acidosis, cardiac arrhythmia, cardiovascular collapse and multi-organ failure).
  ✓ Weak recommendation in favor of the intervention, moderate quality of evidence

• Patients should be closely monitored for the possible occurrence of propofol infusion syndrome (hyperkalemia, metabolic acidosis, cardiac arrhythmia, cardiovascular collapse and multi-organ failure).
  ✓ Good clinical practice.

¹ The use of the Richmond Agitation-Sedation Scale (RASS) for the evaluation and control of sedation is suggested because it is the most widely used scale.
Question 8

In adult patients with severe TBI treated in an ICU, does thrombo-prophylaxis with low molecular weight heparin (LMWH), compared with thrombo-prophylaxis with unfractionated heparin, reduce the presence of thrombotic events and mortality at discharge?

Recommendation

- It is recommended that adult patients with severe TBI receive antithrombotic prophylaxis with low molecular weight heparin (enoxaparin). The suggested dose is 30mg/SC/day.
  ✓ Weak recommendation for intervention, low quality of evidence.

- The recommendation is to start antithrombotic therapy as soon as possible; as long as the patient is not receiving transfusions, is stable in the neurological examination (no reduction in GCS) and that the CT scan shows evidence that the bleeding is controlled (no expansion in the area of bleeding).
  ✓ Weak recommendation for intervention, low quality of evidence

- Start pneumatic compression stockings in patients with severe TBI immediately after admission to the ICU.
  ✓ Good clinical practice.

Question 9

In adult patients with severe TBI being treated in an ICU, does guided therapy with monitoring of intracranial pressure (ICP), compared with treatment without ICP monitoring, reduce mortality at discharge?
Recommendation

- It is suggested that adult patients with severe TBI need to be monitored with intracranial pressure measurement devices when they meet the following criteria: Glasgow Coma Scale greater than or equal to 3 and less than or equal to 8 after resuscitation and an abnormal CT (hematoma, contusion, edema, herniation or compression of basal cisterns).

  ✓ Weak recommendation in favor of intervention, very low quality of evidence.

- It is suggested that treatment of intracranial hypertension be initiated when the value measured in the patient is greater than 20mmHg in a single measurement.

  ✓ Weak recommendation in favor of intervention, Very low quality of evidence.

Question 10

In adult patients with severe TBI being treated in an ICU, does selective head cooling, compared to normothermia, decrease neurological disability and mortality at discharge?

Recommendation

- It is suggested that adult patients with severe TBI have selectively and non-invasively cooled their skulls using a recirculating-water system or tapes chilled to 4 degrees centigrade, ensuring that intracerebral temperature can be measured.

  ✓ Weak recommendation in favor of the intervention, moderate quality of evidence.
• It is suggested that patients should be maintained at a body temperature above 36 degrees and below 38 degrees, measured rectally, in order to avoid systemic hypothermia.

✓ Weak recommendation in favor of the intervention, moderate quality of evidence.

• It is not recommended to perform the intervention in institutions that do not have a recirculating-water system or tapes chilled to 4 degrees centigrade.

✓ Recommendation by strong consensus in favor of the intervention.
The development process began with a selection of questions raised on international guidelines that discuss the same condition and have the same scope, in order to create a starting point for discussion with different actors in the system and discuss priorities adjusted to the Colombian context. The working group made a careful review of the questions included in the most internationally recognized guidelines and made a list of about 34 options of questions on critical issues involving aspects of diagnosis, treatment and rehabilitation of adult patients with severe TBI. These questions took into account that the Colombian guideline would be implemented in an environment with different resources from those in the analyzed literature, since all these came from countries with greater resources in their health systems, especially in such aspects as available technology for advanced monitoring in intensive care units. The aspects related to emergency care system were also taken into account, especially in relation to the care within organized trauma systems. Three surveys aimed at general practitioners, emergency physicians, neurosurgeons and intensivists were performed. From these surveys, the topics, which had most variability in the answers and to which most emphasis was given by respondents, were:

- **Prehospital and Emergency Care:**
  - Prehospital intubation
  - Resuscitation using fluid at prehospital level
  - Use of hyperosmolar solutions in emergency departments
  - Suggested time for surgical interventions
  - Sedation in the emergency department

- **Surgery and Intensive Care**
  - Times and indications for neurotrauma surgery
  - Hyperosmolar solutions in the ICU
- Use of glycemia in the ICU
- Management of hyperthermia in the ICU
- Systemic and selective hypothermia in the ICU
- Thromboprophylaxis in the ICU
- ICP monitoring

With the questions from the guides, in addition to the questions prioritized by surveys, an initial core set of questions was developed; this core set was discussed with different thematic panels including meetings with members of the Colombian Association of Prehospital Care, the Colombian Association of Specialists in Emergency Medicine, the Colombian Association of Neurosurgery and the Colombian Association of Critical Care and Intensive Care Medicine. In two of these meetings, surveys were conducted with specific methods for prioritizing questions in populations of 30 and 20 participants respectively. Following these discussions and in parallel with the work done with the Ministry of Health and the Institute for the Assessment of Technology in Health (IETS) to focus the scope and objectives, the process reached a final number of ten questions, in order to work, using the PICO model, whilst adding an economic question. These questions where focused on aspects of prehospital treatment (intubation and use of resuscitation fluid in prehospital situations) emergency care (use of hyperosmolar solutions), surgery (optimal timing for surgery in subdural & epidural hematoma and for cerebral edema) and intensive care (sedation, thromboprophylaxis, monitoring of intracranial pressure and selective hypothermia). By request of the Ministry of Health and Social Protection, two open (non PICO) questions related to the organization of the health system were included (indications for performing a brain scan on patients with TBI, and reference criteria for these same patients from centers with lower levels of specialization to those with specialized level of care).

**Definition and classification of outcomes**

Given that an extensive literature review of guidelines and articles related to the diagnosis and treatment of adult patients with severe TBI was carried out, the most important outcomes were established considering the methodology suggested by GRADE, including their suggested classification in critical, important but not critical, and low importance. After
discussion with the working group, caregivers, patients, scientific associations and the Ministry of Health and Social Protection, it was concluded that the critical outcomes for all questions corresponded to survival and neurological disability as assessed by specific scales such as the Glasgow Outcome Scale (GOS) and its extended version (GOS-E). These two versions of the same scale allow a classification of 5 and 8 categories respectively, which categorized a bad or good functional outcome.

**TABLE 3. Glasgow Outcome Scale**

<table>
<thead>
<tr>
<th>SCORE</th>
<th>Good recovery. Resumption of normal life. There may be minor neurologic and/or psychological deficits.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Moderate disability (disabled but independent). Independent for daily life activities, although disabled as a consequence of deficits such as hemiparesis, dysphasia, ataxia, intellectual deterioration, memory deficit or personality changes.</td>
</tr>
<tr>
<td>4</td>
<td>Severe disability (conscious but dependent), dependent on others for everyday activities due to physical or mental deficits, or both.</td>
</tr>
<tr>
<td>3</td>
<td>Persistent vegetative state</td>
</tr>
<tr>
<td>2</td>
<td>Dead</td>
</tr>
</tbody>
</table>

**TABLE 4. Extended Glasgow Outcome Scale GOS-E**

<table>
<thead>
<tr>
<th>SCORE</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vegetative state (VS)</td>
</tr>
<tr>
<td>2</td>
<td>Lower severe disability (Lower SD)</td>
</tr>
<tr>
<td>3</td>
<td>Upper severe disability (Upper SD)</td>
</tr>
<tr>
<td>4</td>
<td>Lower moderate disability (Lower MD)</td>
</tr>
<tr>
<td>5</td>
<td>Upper moderate disability (Upper MD)</td>
</tr>
<tr>
<td>6</td>
<td>Lower good recovery (Lower GR)</td>
</tr>
<tr>
<td>7</td>
<td>Upper good recovery (Upper GR)</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
Other critical outcomes for decision making (failed intubation, serum concentrations of triglycerides, deep vein thrombosis and pulmonary embolism) and important, but not critical outcomes for decision making (success rate of intubation at the first attempt, systemic complications in hospitals, progression of neurological damage) were also considered. Due to the above, and thinking that severe TBI is a condition with high rates of mortality and neurologic disability, critical outcomes (mortality/survival and neurological disability), regardless of intermediate outcomes, were prioritized, considering also that any of the interventions that improve survival and neurological disabilities were the most important (especially due to the importance expressed by patients and caregivers regarding the negative results in their quality of life, including the associated disability that may occur as result of severe TBI).

Construction of the set of evidence or de novo development

It was decided to conduct a de novo development taking into account the mechanism suggested by the Methodological Guide for the Elaboration of Clinical Practice Guidelines with Economic Evaluation in the Colombian General Social Security System in Health. As the scope and objectives (adult patients with severe TBI) were focused, searches were aimed at specific PICO questions in this population. The two open questions (indications for performing a brain scan in patients with TBI and criteria for referral of these same patients, from less specialized levels to more specialized centers of care) were answered through specific searches that covered adult patients with mild to moderate trauma. The search strategy included international databases in English and Spanish, gray literature searches and discussions with experts in order to search for additional sources of scientific associations and summaries of academic events specialized in the subject. This literature search included studies from 1 January 2000 to July 7 of 2013. Once the search syntax was designed, this was sent to the Iberoamerican Cochrane Centre for review, where suggestions were made to adjust them. The databases searched were PUBMED, EMBASE, COCHRANE LIBRARY, Tripdatabase, and DIMDI (MedPilot, SCISEARCH and BIOSIS). Other searches included, Google Scholar, unindexed Latin American biomedical journals and pages of national and international
scientific associations in the area. General search criteria for inclusion considered: patients older than 15 years with severe TBI, scoring less than 9 on the Glasgow Coma Scale (GCS) or with an Injury Severity Score (AIS) for the head higher than 2. Articles that included patients under 16 years old and patients with mild to moderate trauma (with the exception the criterion of severity in question 1) were excluded. The filters used were the following: Article Types: Clinical Trial, Comparative Study, Controlled Clinical Trial, Evaluation Studies, Guideline, Meta-Analysis, Multicenter Study, Practice Guideline, Randomized Controlled Trial, Review, Systematic Reviews, Technical Report, Validation Studies. Publication dates: 01/01/2000 to 07/07/2013. Species: Humans. Languages: English, Spanish. Sex: Female, Male. Journal categories: Core clinical journals and MEDLINE.

**Inclusion process for articles**

Articles were included if they had recommendations for clinical practice in the treatment of severe TBI according to the selected PICO questions. Articles that did not consider the specified population were excluded, as were articles addressing other issues, editorials, letters to editors, non-systematic reviews, studies being developed but without published results, case reports and reviews of articles. If multiple versions of the same article were available, the latest version was selected. Once the criteria for inclusion and exclusion of studies for each question were defined, the evaluators performed a review of titles and abstracts.

**Quality assessment of studies for inclusion**

For the assessment of the methodological quality of the selected studies, the formats proposed by SIGN (Scottish Intercollegiate Guidelines Network) were used. They were translated into Spanish following the Methodological Guideline for the Elaboration of Clinical Practice Guidelines with Economic Evaluation in the Colombian General Social
Security System for Health. Within these formats, checklists were included for each question, according to the type of study selected (systematic review and meta-analysis, controlled clinical studies, cohort studies, case studies and controls).

**Process of information extraction and evidence synthesis**

The exercise of evidence extraction was performed with clinical experts from the working group whose topic of expertise matched the specific subject. The same exercise was conducted in parallel with methodological group of the working group. In this way, it was possible to double check the extraction process in order to subsequently access the data required for making the tables of evidence.

**Final assessment of the body of evidence**

The GRADE approach was used to define levels of quality of evidence (high, moderate, low and very low). The parameters used after initial evaluation of the body of evidence according to the study design were: risk of bias, inconsistency, direct or indirect evidence, inaccuracy and risk of selective publication of outcomes. The magnitude of the effect, the dose-response relationship and any possible residual confusion and residual bias were also taken into account. Following the GRADE recommendations, randomized trials were considered of high quality while observational studies were considered of low quality. The type of articles found did not allow the realization of meta-analyses for any questions. The ratings of the evidence with their meaning and graphical interpretation are presented in Table 5:
TABLE 5. Definition of levels of evidence

<table>
<thead>
<tr>
<th>LEVEL OF EVIDENCE</th>
<th>DEFINITION</th>
<th>GRAPHIC REPRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Se tiene gran confianza en que el verdadero efecto se encuentra cerca al estimativo del efecto.</td>
<td>🟠🟠🟠🟠</td>
</tr>
<tr>
<td>Moderate</td>
<td>There is moderate confidence in the estimate of the effect: it is likely that the true effect is close to the estimate of the effect, but the possibility exists that it is substantially different.</td>
<td>🟠🟠🟠🟠</td>
</tr>
<tr>
<td>Low</td>
<td>Confidence in the estimate of the effect is limited: the true effect may be substantially different from the estimate of the effect.</td>
<td>🟠🟠🟠🟠</td>
</tr>
<tr>
<td>Very Low</td>
<td>One can have very little confidence in the estimate of the effect: it is likely that the true effect is substantially different from the estimate of the effect.</td>
<td>🟠🟠🟠🟠</td>
</tr>
</tbody>
</table>

The final rating of the body of evidence was made by the metodological experts of the working group together with the working group of the Iberoamerican Cochrane Center in Spain.

Formulation of recommendations

For the formulation of the recommendations, the GRADE methodology, which identifies four determinants for the direction and strength of recommendations, was used. These are:

- Balance between desirable and undesirable results (estimated effects), with consideration of the values and preferences. The smaller the difference is, the less likely it is that a strong recommendation will be made.
- Confidence in the magnitude of the estimated effect of the intervention on important outcomes. If confidence is low, it is less likely that a strong recommendation will be made.
- Confidence in values, preferences and variability. The lower the confidence or the greater the variability, the less likely it is that a strong recommendation will be given.
• Use of resources. When resource use is higher, it is less likely that a strong recommendation will be made.

Each recommendation that was made was given a strength (strong, weak) and directionality (in favor of making an intervention or against making it). The evidence on which it is based was described as high, moderate, low or very low according to the GRADE system.

**Patient participation**

In the development process of the guideline, patients and their families were invited to two meetings (Table 6). Both patients and caregivers mentioned the importance that health professionals make decisions in a timely manner and using appropriate clinical criteria in order to cause a better outcome. Detailed information regarding the preferences of patients for each of the questions is addressed in the discussion of each question, including its effect on the recommendations.
### TABLE 6. Format of the report into patient participation in the development of the CPG

<table>
<thead>
<tr>
<th>STAGE IN THE DEVELOPMENT OF THE CPG</th>
<th>STRATEGIES FOR PATIENT PARTICIPATION</th>
<th>RESULT: SUMMARY OF INFORMATION FOUND</th>
<th>INCORPORATION: DESCRIPTION OF THE INFORMATION INCLUDED AND NOT INCLUDED, AND THE REASONS FOR NOT DOING SO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of the scope of the CPG</td>
<td>Questionnaire</td>
<td></td>
<td>The scope of the guide was briefly described, in terms of the topics that were found to be of relevance to patients.</td>
</tr>
<tr>
<td>Formulation of questions</td>
<td>Questionnaire</td>
<td></td>
<td>The potential questions were included and those that resulted being too technical and that could distort the information for patients were explained more simply.</td>
</tr>
<tr>
<td>Identification and evaluation of outcomes.</td>
<td>Questionnaire</td>
<td></td>
<td>This stage addressed the outcomes produced by the working group and that were found to be of relevance for patients and relatives.</td>
</tr>
<tr>
<td>Formulation of recommendations</td>
<td>Questionnaire</td>
<td></td>
<td>Patients and their carers made contributions that helped or modified the recommendations made by the working group.</td>
</tr>
<tr>
<td>STAGE IN THE DEVELOPMENT OF THE CPG</td>
<td>STRATEGIES FOR PATIENT PARTICIPATION</td>
<td>RESULT: SUMMARY OF INFORMATION FOUND</td>
<td>INCORPORATION: DESCRIPTION OF THE INFORMATION INCLUDED AND NOT INCLUDED, AND THE REASONS FOR NOT DOING SO.</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------------------------------------</td>
<td>-------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Revision of the preliminary documents of the CPG.</td>
<td>Participation: The document was socialized with patients and their families. Questionnaire: this was done through a survey and sending the document to a group of patients and relatives.</td>
<td>By consulting with patients through a survey, it was shown that for them it is very important that skilled professionals are responsible for patients with severe TBI and they are told about the techniques of coping with this situation.</td>
<td>The elements that are of most relevance to patients and their relatives are included, taking into account: The accompaniment and the role to be performed by the family as part of in-hospital and post-discharge treatment.</td>
</tr>
<tr>
<td>Construction of the guide for patients.</td>
<td>Participation: both family and patients were invited to help with the structuring of the document. Questionnaire: the mechanism was an informal interview since there is a database of patients who have suffered severe TBI and have been treated at Neiva hospital during the last 5 years</td>
<td>The entire contents of the patients' version of the CPG obeyed the need that patients and their relatives have for information.</td>
<td>Aspects of the treatment of patients prehospital, as inpatients and after discharge were included. No technical information was included regarding specific clinical procedures due to the lack of understanding of this information by patients and family.</td>
</tr>
<tr>
<td>Formulation of indicators and implementation</td>
<td>Questionnaire: the mechanism was an informal interview.</td>
<td>The contributions of the patients did not generate any changes to the indicators proposed by the working group.</td>
<td></td>
</tr>
</tbody>
</table>
Questions, evidence and recommendations

Question 1a

Which patients with TBI should have a computerized tomography (CT) of the head?

Recommendation

- It is recommended that every adult patient with TBI and who meet one or more of the following criteria must be have a CT scan:
  - Skull fracture (clinical or radiological) including signs of basilar skull fracture (periorbital ecchymosis, retroauricular ecchymosis, otorrhea, rhinorrhea).
  - Post-traumatic seizure
  - Focal neurological deficit
  - Persistent vomiting (greater than or equal to two episodes)
  - Drop in the Glasgow Coma Scale of at least 1 point
  - Previous craniotomy
  - When the patient is a pedestrian who was hit by a car.
  - History of coagulopathy or pharmacologic anticoagulation
  - Patients suspected to be intoxicated.
  - Fall from height greater than 1.5 m
  - Retrograde Amnesia> 30 minutes and/or anterograde
  - Age greater than or equal to 60 years.
  - Severe headache
  - Blurred vision or diplopia
**Introduction**

Intracranial injuries following a TBI can be detected using imaging, even before the manifestations of clinical signs. If a patient with mild TBI (Glasgow 13-15) arrives at a health institution that does not have the facilities to perform imaging (CT scan), there is an important difference in the clinical practice in terms of decision making so that patients who require this scan can be transferred promptly. Furthermore, even in institutions that have these facilities, there are discrepancies in the criteria for carrying out the exam on patients with mild TBI. Therefore, it is considered important to ask this question.

**Summary of the evidence**

Through the search strategy described in annex 6, only one study with acceptable methodological quality was found, and this was evaluated through the SIGN meta-analysis instrument. This meta-analysis (Pandor 2012) included 71 studies analyzed in two separate groups (a group of 42 adults and a group of 29 children), evaluating the sensitivity, specificity and positive and negative likelihood ratio for 32 clinical variables including injury mechanism and its relationship with a positive outcome after an intracranial injury or one that requires neurosurgery. According to the results of the mentioned imaging, the clinical elements were divided into those with greater possibility of association with injury (skull fracture and post-traumatic seizure) moderate possibility of association with injury (focal deficit, persistent vomiting, fall on the Glasgow scale, previous neurosurgery) and low possibility of association with injury (high fall, coagulopathy, chronic use of alcohol, age over 60, injury due to being struck by a car, vomiting and retrograde amnesia).

The sensitivity, specificity and likelihood ratio results for each of the clinical variables, specifically for findings of intracranial injury on the scans, are summarized in Table 7.
### TABLA 7. Summary of the results of the meta-analysis made by Pandor 2012; findings of each clinical variable for a diagnosis of intracranial injury in adults with mild TBI (sensitivity, specificity, LR+ and LR- grouped).

<table>
<thead>
<tr>
<th>CLINICAL CHARACTERISTIC</th>
<th>NO. OF STUDIES</th>
<th>NO. OF PATIENTS</th>
<th>SENSITIVITY</th>
<th>SPECIFICITY</th>
<th>LR(-)</th>
<th>LR(+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 60 years old</td>
<td>7</td>
<td>20,514</td>
<td>23,9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>88,0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,868</td>
<td>1,97</td>
</tr>
<tr>
<td>Anterograde or postraumatic amnesia</td>
<td>6</td>
<td>16,965</td>
<td>16,2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>91,9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,912</td>
<td>1,95</td>
</tr>
<tr>
<td>Basilar skull fracture</td>
<td>8</td>
<td>27,717</td>
<td>21,1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>98,4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,80</td>
<td>54,070</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>8</td>
<td>35,567</td>
<td>4,9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>98,2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,968</td>
<td>3,27</td>
</tr>
<tr>
<td>Depressed fracture of the skull</td>
<td>2</td>
<td>2680</td>
<td>9,1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>99,9</td>
<td>0,967</td>
<td>102,15</td>
</tr>
<tr>
<td>Fall from height</td>
<td>1</td>
<td>1064</td>
<td>28,0</td>
<td>87,8</td>
<td>0,820</td>
<td>2,29</td>
</tr>
<tr>
<td>Neurological focal deficit</td>
<td>8</td>
<td>21,729</td>
<td>6,6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>98,6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,95</td>
<td>9,671</td>
</tr>
<tr>
<td>Reduction on the Glasgow Coma Scale</td>
<td>3</td>
<td>6365</td>
<td>27,3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>95,7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,763</td>
<td>6,39</td>
</tr>
<tr>
<td>Intoxication</td>
<td>10</td>
<td>31,156</td>
<td>21,4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>84,6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,931</td>
<td>1,38</td>
</tr>
<tr>
<td>Collision with vehicle</td>
<td>6</td>
<td>6716</td>
<td>15,9</td>
<td>95,4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,882</td>
<td>3,43</td>
</tr>
<tr>
<td>Persistent vomiting</td>
<td>4</td>
<td>29,556</td>
<td>16,1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>97,2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,871</td>
<td>5,53</td>
</tr>
<tr>
<td>Post-traumatic seizure</td>
<td>2</td>
<td>11,076</td>
<td>7,9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>99,4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,921</td>
<td>12,39</td>
</tr>
<tr>
<td>Previous neurosurgery</td>
<td>3</td>
<td>19,056</td>
<td>1,9</td>
<td>99,8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,985</td>
<td>8,67</td>
</tr>
<tr>
<td>Fracture on skull x-ray</td>
<td>8</td>
<td>6502</td>
<td>29,8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>97,4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,720</td>
<td>14,26</td>
</tr>
<tr>
<td>Retrograde amnesia</td>
<td>4</td>
<td>14,023</td>
<td>44,3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>81,6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,687</td>
<td>2,41</td>
</tr>
<tr>
<td>Persistent or severe cefalea</td>
<td>2</td>
<td>15,871</td>
<td>19,4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>80,5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1,028</td>
<td>1,00</td>
</tr>
<tr>
<td>Visual problems (diplopia)</td>
<td>3</td>
<td>664</td>
<td>2,4</td>
<td>94,2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1,033</td>
<td>0,39</td>
</tr>
</tbody>
</table>

<sup>c</sup> significant heterogeneity, Value of P <0.05
From evidence to recommendation
The discussion with the members of the working group considered all the criteria associated with risk of intracranial injury considering the importance of this study for the referral process for patients within the health system. It took into account the availability and importance of the CT scan at a national level.

Structural requirements
This guide considers that, in order to carry out this recommendation, it is vital to have personnel who are suitably trained in the identification of these risk factors. These same factors must be considered during the development of clinical history forms in emergency departments at any level of complexity.

Considerations on benefits and risks
It is considered that the benefit of opportune identification and treatment of an intracranial injury outweighs the risk of the ionizing radiation associated with the taking of a brain scan.

Considerations on values and preferences of patients
Patients and their caregivers stated a clear preference for the opportunity for early access to a definitive care center, one which has a level of specialization that is suitable for all the interventions that are required, as soon as possible after the injury.

Implications on resources
It is considered that the benefit of applying the recommendation can be cost effective, taking into account that the cost of a brain scan is less than the cost of an unidentified, untreated intracranial injury. It should be taken into account that in Colombia there are no economic studies on the implications of this intervention.

References
Flowchart for the process of inclusion in articles

References identified through searches of databases (n=261)
- Pubmed: 175
- Embase: 26
- Biosis: 19
- Scisearch: 20
- Medpilot: 10
- Cochrane: 1
- Tripdatabase: 10

References obtained manually (n=1)

All references obtained (n=262)

Duplicate References (n=7)

References included with title and abstract that were revised (n=255)

Articles not related (n=254)

Revised Articles (n=1)

Excluded articles (n=0)

Included articles (n=1)
Algorithm 1

Transfer to high-level centers (questions 1a and 1b)

1. Perform Glasgow Coma Scale

   - Adult patient with TBI
     - Mild (13-15)
       - Yes: Meets criteria of CT*
         - Transfer to high complexity center with emphasis on trauma care
       - No: Continue management in Center of low to medium complexity
     - Moderate-Severe (3-12)
       - Yes: Meets criteria for transfer**
         - Transfer to high complexity center with emphasis on trauma care
       - No: Continue management in Center of low to medium complexity

*Criteria of CT
- Skull fracture (clinical or radiological) including signs of fracture of the skull base (periorbital ecchymosis and ecchymosis headpiece, otoliquia, rinoliquia).
- Traumatic seizure
- Focal neurologic deficit
- Persistent vomiting (greater than or equal to two episodes)
- Fall of the Glasgow of at least 1 point
- Previous Craniotomy
- Mechanism of the trauma produced by runover in condition of pedestrian
- History of coagulopathy or pharmacological anticoagulacion
- Patient with suspected poisoning
- Fall from height greater than 1.5 meters
- Retrograde Amnesia > 30 minutes and/or anterograde
- Age greater than or equal to 60 years
- Severe headache
- Blurred vision or diplopia

**Transfer criteria
- Glasgow under 15 up to 2 hours after the injury
- Severe headache
- Persistent vomiting (greater than or equal to two episodes)
- Skull fracture (clinical or radiological) including signs of fracture of the skull base (periorbital ecchymosis and ecchymosis headpiece, otoliquia, rinoliquia).
- Age greater than or equal to 60 years
- Blurred vision or diplopia
- Traumatic seizure
- Focal neurologic deficit
- Previous Craniotomy
- Fall from height greater than 1.5 meters
- Retrograde Amnesia > 30 minutes and/or anterograde
- Suspicion of intoxication with alcohol and/or psychoactive substances
Question 1b

Which patients with TBI should be transferred from low-level of care hospitals to centers with neurosurgery and neuroimaging services?

Recommendation

- It is recommended that patients with moderate to severe TBI (Glasgow 3-12) should be transferred immediately to high-level of care hospitals with access to neuroimaging and neurosurgery.

- It is recommended that patients with mild TBI (Glasgow 13-15) who present one or more of the following criteria be referred for evaluation at an institution that has access to neuroimaging and neurosurgery:
  - Glasgow coma score under 15 up to 2 hours after injury
  - Severe headache
  - More than 2 episodes of vomiting
  - Skull fracture, including depressed fractures or clinical signs of fracture of the skull base (raccoon eyes, retro auricular ecchymosis, otorrhea or rhinorrhea)
  - Age greater than or equal to 60 years old
  - Blurred vision or diplopia
  - Post-traumatic seizure
  - Focal neurological deficit
  - Previous craniotomy.
  - Fall of over 1.5 meters.
  - Retrograde amnesia more than 30 minutes and/or anterograde amnesia.
  - Suspected intoxication with alcohol and/or psychoactive substances.

- It is recommended that patients with mild TBI and who are in active treatment with anticoagulants, have active coagulopathies, or are pregnant should be transferred to centers with neurosurgery and neuroimaging services.
Introduction

Currently, several health institutions in Colombia do not have a specialized trauma department for evaluation and decision-making in relationship with the heterogeneous group that involves patients with TBI. Usually patients with moderate to severe TBI (Glasgow 3-12) are transferred immediately due to the clear need for diagnostic imaging of the brain. The greatest variability in the criteria for transfer of patients is in those with mild TBI (Glasgow 13-15). The vast majority of low and medium complexity centers, especially rural hospitals, do not have a scanner available which could support prognostics or therapeutic decisions and for this reason it is important to establish what clinical criteria correlate with the presence of intracranial injury in patients with mild TBI. Because of this reality in terms of disparity of resources, this situation raises the need to define which patients should be transferred to a higher level of care center and when. For this reason, it was considered important to analyze the current evidence to establish clinical and imaging criteria for referring patients with TBI to neurosurgical services.

Summary of the evidence

Through the search strategy described in Annex 6, a meta-analysis was identified (Dunning 2004) that evaluated studies on prognostic factors, indicating the relative risk that a person with certain clinical findings has of developing any intracranial pathology. Additionally, a systematic review was found (Harnan 2011), which included analyses of diagnostic accuracy of different clinical rules for decision making in patients with mild TBI who are at risk of intracranial injury. After the analysis of the two studies, the final recommendation was made based on a systematic review of Harnan, 2011. The reason for choosing this study (which assesses more recent evidence than the meta-analysis and which presents an acceptable methodological quality evaluated using the AMSTAR methodology) was based on that fact that the clinical decision algorithms discussed in this paper can be used in our environment, in accordance with the technology available in Colombia and the characteristics of the care system. This review examined 19 studies that reported accurate data regarding 25 decision rules. Of these, 9, which all specified neurosurgical outcomes, were reported including groups of high and medium risk. The decision rules were intended to identify those adult patients with TBI who are at risk of an injury requiring neurosurgical intervention (considered high risk) and tho-
These patients at risk of intracerebral injury (considered medium risk). 11 rules were evaluated using more than one database and one rule was evaluated in two cohorts. The criteria for the decision rule called “Canadian CT Head Rule,” which includes aspects of high risk (neurosurgical intervention outcome) and medium risk (intracerebral injury outcome) showed a sensitivity of 99% to 100% for both aspects, and a specificity of 48% -77% in high-risk patients and 37% to 48% for medium-risk patients. This was the rule with the best psychometric properties (sensitivity and specificity) in patients with mild TBI (Glasgow 13-15). The exclusion criteria of the study were rather strict and included patients less than 16 years old, people with mild TBI without loss of consciousness, TBI with penetrating head injury, patients with focal deficits, hemodynamically unstable patients, patients using oral anticoagulants, patients with seizures before entering the emergency room, patients who were readmitted on the same day of the trauma or pregnant patients. The criteria of the “Canadian CT Head Rule” are presented in Table 8.

**TABLE 8. Canadian CT Head Rule.**

<table>
<thead>
<tr>
<th>HIGH RISK (FOR NEUROSURGICAL INTERVENTION)</th>
<th>MEDIUM RISK (FOR BRAIN INJURY DETECTION BY CT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Glasgow coma scale&lt;15 at 2 hours after injury</td>
<td>1. Amnesia before impact of ≥ 30 minutes</td>
</tr>
<tr>
<td>2. Suspected open or depressed skull fracture.</td>
<td>2. Dangerous mechanism (pedestrian hit by a car, occupant thrown out of a motor vehicle or fall ≥ 3 feet or 5 stairs).</td>
</tr>
<tr>
<td>3. Any sign of basal skull fracture (hemotympanum, raccoon eyes, otorrhea, rhinorrhea or retroauricular bruising)</td>
<td></td>
</tr>
<tr>
<td>4. 2 or more episodes of vomiting</td>
<td></td>
</tr>
<tr>
<td>5. 65 years or older</td>
<td></td>
</tr>
</tbody>
</table>

**THIS RULE IS NOT APPLICABLE IN CASES OF:**
- Non-traumatic cases
- Glasgow coma scale< 13
- Age < 16 years
- Patients treated with warfarin or with coagulation disorder
- Obvious open skull fracture
The full group of evaluated rules is presented in table 9.

**TABLA 9. Sensitivity and specificity of the decision rules to identify injuries that require neurosurgical intervention**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>SENSITIVITY</th>
<th>SPECIFICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCHR High Risk</td>
<td>0.99 - 1.00</td>
<td>0.48 - 0.77</td>
</tr>
<tr>
<td>New Orleans Criteria</td>
<td>0.99 - 1.00</td>
<td>0.04 - 0.31</td>
</tr>
<tr>
<td>New Orleans Criteria adapted to cohort</td>
<td>1.00</td>
<td>0.03</td>
</tr>
<tr>
<td>CCHR High and Medium Risk</td>
<td>0.99 - 1.00</td>
<td>0.37 - 0.48</td>
</tr>
<tr>
<td>CCHR High and Medium Risk adapted to cohort</td>
<td>1.00</td>
<td>0.37</td>
</tr>
<tr>
<td>NCWFNS High and Medium Risk</td>
<td>0.94 - 0.99</td>
<td>0.03 - 0.44</td>
</tr>
<tr>
<td>NICE lenient criteria</td>
<td>0.94 - 0.98</td>
<td>0.29 - 0.67</td>
</tr>
<tr>
<td>Scandinavian lenient criteria</td>
<td>0.94 - 0.99</td>
<td>0.20 - 0.50</td>
</tr>
<tr>
<td>Miller criteria</td>
<td>0.50 - 1.00</td>
<td>0.61 - 0.66</td>
</tr>
</tbody>
</table>

*CCHR (Canadian CT head rule), NCWFNS (Neurotraumatology Committee of the World Federation of Neurosurgical Societies).*

**From evidence to recommendation**

The discussion with the working group took into account the system of reference and counter-reference established within the legal framework of the General System of Social Security in Colombia and the aspects of cost and availability of resources together with the component of patient safety. It was considered important to combine the evidence recommended in order to make neurological scans with those recommended for assessment for neurosurgery. Two groups were established according to the level of severity of the injury (Glasgow 3-12 and Glasgow 13-15) and specific recommendations were constructed based on these.

**Structural requirements**

It is considered that to carry out this recommendation, there is a need to have personnel properly trained in identifying these risk factors. These same factors must be taken into account during the development of medical history formats in emergency services of any complexity.
Considerations on benefits and risks
It is considered that the benefit of the identification and prompt treatment of an intracranial lesion outweighs the risk that a process of referral to a higher level of complexity might implicate.

Considerations on the values and preferences of patients
The patients and their caregivers expressed a clear preference for the opportunity for early access to a definitive care center, which includes the appropriate level of complexity for all interventions that may be required, as soon as possible after injury.

Implications on resources
It is considered that the benefit of implementing the recommendation may be cost effective, given that the cost of an unidentified intracranial injury without appropriate treatment can be much higher than the cost of the referral process. It is important to keep in mind that there are no economic studies on the implications of this recommendation in Colombia.

References
Flowchart for the process of inclusion in articles

References identified through searches of databases (n=134)
- Pubmed: 95
- Embase: 0
- Scisearch: 11
- Medpilot: 16
- Cochrane: 3
- Tripdatabase: 8

References obtained manually (n=2)

All references obtained (n=136)

Duplicate References (n=7)

References included with title and abstract that were revised. (n=129)

Articles not related (n=127)

Revised Articles (n=2)

Excluded articles (n=1)

Included articles (n=1)
Algorithm 1

Referrals to high-level centers (questions 1a and 1b)

Adult patient with TBI

Perform Glasgow Coma Scale

Mild
13-15

Moderate-Severe
3-12

Meets criteria of CT*

Transfer to high complexity center with emphasis on trauma care

Meets criteria for transfer**

Continue management in Center of low to medium complexity

*Criteria of CT
- Skull fracture (clinical or radiological) including signs of fracture of the skull base (periorbital ecchymosis and ecchymosis headpiece, otoliquia, rinoliquia).
- Traumatic seizure
- Focal neurologic deficit
- Persistent vomiting (greater than or equal to two episodes)
- Fall of the Glasgow of at least 1 point
- Previous Craniotomy
- Mechanism of the trauma produced by runover in condition of pedestrian
- History of coagulopathy or pharmacological anticoaugulacion
- Patient with suspected poisoning
- Fall from height greater than 1.5 meters
- Retrograde Amnesia > 30 minutes and/or anterograde
- Age greater than or equal to 60 years
- Severe headache
- Blurred vision or diplopia

**Transfer criteria
- Glasgow under 15 up to 2 hours after the injury
- Severe headache
- Persistent vomiting (greater than or equal to two episodes)
- Skull fracture (clinical or radiological) including signs of fracture of the skull base (periorbital ecchymosis and ecchymosis headpiece, otoliquia, rinoliquia).
- Age greater than or equal to 60 years
- Blurred vision or diplopia
- Traumatic seizure
- Focal neurologic deficit
- Previous Craniotomy
- Fall from height greater than 1.5 meters
- Retrograde Amnesia > 30 minutes and/or anterograde
- Suspicion of intoxication with alcohol and/or psychoactive substances
**Question 2**

In adult patients with severe TBI, does the treatment in an organized trauma care center, compared to treatment in a general non-specialized center reduce mortality?

**Recommendation**

- It is suggested that adult patients with severe TBI be transferred directly to a leading high-complexity institution with emphasis on trauma care.

  ✓ Weak recommendation in favor of intervention, low quality evidence.

**Introducción**

The organization and development of trauma care systems have been related to a reduction in the rates of mortality and disability for this condition (Mendelof 1991, Sampallis 1997, Maconel 2005, MacKenzie 2006, Rubiano 2013). Patients with severe TBI benefit equally from the organization and development of trauma care systems. Therefore, this type of recommendation has been established in consensus documents and treatment guidelines in different parts of the world (Mass 1997, BTF 2007, Shima 2010). Regional hospitals and clinics with organized trauma care systems (including intensive care units specialized in trauma, residency programs with emphasis on trauma, active processes of education and research in trauma and surgical teams with training in trauma) and high volumes of patients admitted per year (more than 1200 admissions of trauma patients per year or at least 240 admissions with injury severity scores greater than 15), have been associated with a reduction in complications in the treatment of patients with severe TBI. The presence of neurosurgeons and neurointensive care units within these organizations generate additional benefits for patients who have been transferred from institutions that do not have this resource, especially related to the proper management of the airway, early correction of hypotension and early management of intracranial hypertension. Due to the high variability in healthcare resources because of the lack of organization of specific trauma care systems in Colombia, it was considered very important to define whether
the treatment of adult patients with severe TBI in organized trauma care centers vs the treatment of adult patients with severe TBI in centers with lower level of organization reduces mortality and associated complications.

Summary of the evidence
There are few international rankings for determining characteristics of organized trauma care systems. One of the most used rankings is the classification suggested by the Committee on Trauma of the American College of Surgeons (2006). They have developed a system to classify institutions by their ability to serve trauma patients with the aim of helping communities in the organization and development of these systems. In accordance with this classification, this guide recognizes three levels. The highest level of specialization corresponds to a renowned institution or a center of greater specialization that serves as a reference point for other levels of care. Medium specialized levels are centers that serve as the starting point for referrals, especially from rural areas, and the low level of specialization is the closest point of care to where the event occurred. Each of these levels has been assigned characteristics, which are as follows:

High-specialized level
- In house 24 hours a day for general surgery and immediate availability of other specialists such as orthopedics, neurosurgery, anesthesiology, emergency medicine, radiology, internal medicine, plastic surgery, maxillofacial surgery, and adult and pediatric intensive care.
  - A referral center for the community from nearby regions.
  - A leading center in prevention and public education for the community.
  - Provides continuing education to members of the trauma team.
  - Includes a trauma quality improvement program.
- Performs organized activities in teaching and research that help to innovate in trauma care.
  - Has screening programs for substance abuse and intervention.
- Meets minimum requirements in terms of the annual volume of admissions of severely traumatized patients.
Medium-specialized level

- Immediate 24-hour coverage by general surgeons, and coverage of specialties such as orthopedics, neurosurgery, anesthesiology, emergency medicine, radiology and intensive care.
- Other services such as cardiac surgery, hemodialysis and microvascular surgery should be referred to the high-specialized level institutions.
- Provide trauma prevention services and have continuing education programs for their staff.
  - Has a trauma quality improvement program.

Low-specialized level

- Immediate 24-hour coverage by emergency doctors and immediate availability of surgeons and anesthesiologists.
  - Has a trauma quality improvement program.
- Has an organized referral system for patients requiring transfers to medium and high-specialized level institutions.
  - Serves as a support center for rural and community hospitals.
- Provides continuing education for nurses and other members of the trauma team.
  - Engages in prevention programs for their community.

A literature search revealed only one observational database analysis study that could give an answer to the PICO question (DuBose 2008). Additionally, an ongoing randomized study was found (HITS-NS), but being an ongoing study, no preliminary data had been published. This study compares adult patients with moderate to severe TBI who are transported to the nearest center vs those transferred to specialist neurosurgical centers and is in the pilot feasibility phase, waiting to randomize 350 patients in each arm of the study. The DuBose study analyzed 16,035 patients with severe TBI, defined by having a head AIS greater than or equal to 3 without severe injuries to other body parts. These patients were treated in 71 high-specialized trauma institutions and 55 medium specialized institutions. The study found higher rates of mortality and complications in medium specialized institutions. Mortality was 9.6% in the high-specialized centers and 13.9% in medium specialized centers. The rate of complications in more complex centers was 10.6% and in medium complexity centers it was 15.5%. It was found that the progression of neurologic injury (given
by progression of secondary injury mechanisms such as hypotension and hypoxemia) was higher in medium specialized institutions (2% vs 1%). In the analysis of independent risk factors for mortality, it was found that the simple fact of being admitted to a medium specialized institution was a risk factor as important as the fact of being admitted with a penetrating mechanism, having a higher rate of severity, suffering from hypotension or having a low Glasgow score.

**From evidence to recommendation**

During the meeting with the working group, it was considered that this is a weak recommendation for intervention because the balance between the desired result (reduction in mortality and complications at discharge) vs unwanted effects (increased mortality and complications at discharge) is slightly in favor of the first one. The discussion took into account the aspects of cost and availability in the General System of Social Security in Health (GSSSH) and the integration of current evidence from organized trauma care systems within the national system was considered to be an important aspect. Therefore, criteria for good clinical practice, which should be met by high-specialized centers with emphasis on trauma care, were established. It was felt that renowned public and private centers that handle high volumes of patients with trauma could therefore be defined as organized care centers if they meet the criteria associated with good clinical practice.

**Structural requirements**

Given that the Colombian GSSSH currently organizes health care facilities as having low, medium or high complexity, and there are some eligibility criteria for each of these levels, it is considered that to carry out this recommendation, there is already an organizational structure, supported by current regulations, that is equivalent to the criteria set earlier. The criteria recommended and established in the studies that were reviewed include:

- Permanent presence (24 hours) of general surgeons with training in trauma, immediate availability of specialists in orthopedics, neurosurgery, anesthesiology, emergency medicine, radiology, internal medicine, plastic surgery, oral and maxillofacial surgery and critical care.
- Being a center of reference for hospitals with lower level of complexity.
• Providing a leading process in prevention and public education for the region.
• Providing permanent continuing education for members of the trauma care team.
• Including a quality improvement program in trauma care, including review panels for preventable deaths and periodic meetings on morbidity and mortality in trauma; Leading processes in education and research in trauma that generate innovation in the topic.
• Having screening programs for substance abuse and intervention for these patients.
• Meets minimum requirements in terms of the annual volume of admissions of severely traumatized patients (more than 1200 admissions of trauma patients per year or at least 240 admissions with AIS greater than 15).

Considerations on benefits and risks
It is considered that the benefit of prompt and comprehensive treatment of an intracranial injury does not carry any risk that should be assumed by the care system.

Considerations on the values and preferences of patients
Patients and their caregivers expressed a clear preference for the opportunity to access advanced comprehensive care, including that the personnel performing the procedures have an appropriate level of training for all interventions that are required, as soon as possible after injury. There was for this reason, no consideration that amended the recommendations.

Implications on resources
It is considered that the benefit of implementing the recommendation can be cost effective, considering that the cost of an intracranial lesion without proper treatment can be much greater than the cost involved in any minimum changes in the regulations of the system. It is important to keep in mind that there are no economic studies on the implications of this recommendation in Colombia.
References
Flowchart for the process of inclusion in articles

References identified through searches of databases
(n=256)
- Pubmed: 192
- Embase: 41
- Biosis: 2
- Scisearch: 4
- Medpilot: 13
- Cochrane: 3
- Tripdatabase: 1

References obtained manually
(n=1)

All references obtained
(n=257)

Duplicate References
(n=4)

References included with title and abstract that were revised
(n=253)

Articles not related
(n=252)

Revised Articles
(n=1)

Included articles
(n=1)
Question 3

In adult patients with severe TBI, does prehospital orotracheal intubation, compared with orotracheal intubation in emergency departments, reduce neurological disability or mortality, evaluated at 6 months post-injury?

Recommendation

- It is recommended that adult patients with severe TBI need to be intubated in the trachea in a prehospital setting, using a rapid sequence intubation, which includes inductor medication and neuromuscular paralysis medication.
  ✓ Strong recommendation in favor of intervention, moderate quality of evidence.

- The recommended dosages to be used are the following:
  - Fentanyl Dose: 1 μg/Kg
  - Midazolam Dose: 0.1mg/Kg
  - Succinylcholine Dose: 1 mg/Kg
  ✓ Strong recommendation in favor of intervention, moderate quality of evidence.

- The use of half the dose of inductor medications suggested above is recommended if the patient has systolic blood pressure <100mmHg, or is >60 years old.
  ✓ Strong recommendation, moderate quality of evidence

- Orotracheal intubation in a prehospital setting should be carried out by skilled medical personnel or prehospital technologists (who have an adequate level of training). Technologists must carry out the procedure under direct or indirect supervision of a doctor with experience in handling prehospital and in-hospital emergencies.
  ✓ Weak recommendation in favor of intervention, low quality of evidence.
• We suggest that adequate training as part of intubation training programs should be considered to be at least 16 hours of theoretical-practical training in rapid sequence intubation, including at least 4 hours of theory, 8 hours of experience in intubation in operating theaters under the supervision of an anesthesiologist and at least 4 hours of evaluation in simulators.
  ✔ Weak recommendation, moderate quality of evidence.

• It is recommended that if the attempt to intubate is not successful, patients should continue to be ventilated with a bag valve mask system, together with an oropharyngeal airway, until they return to spontaneous respiration. If this method is insufficient to achieve a pulse oximetry >90%, we recommend the use of a laryngeal mask, as a rescue device.
  ✔ Strong recommendation in favor of intervention, moderate quality of evidence.

• It is suggested that in the case that the patient is being moved by a basic ambulance, and there is no technologist or medic on board, ventilation should be carried out with a bag valve mask system, together with an oropharyngeal airway in order to achieve a pulse oximetry of >90%.
  ✔ Good clinical practice

Introduction
Hypoxia, defined as a lack of oxygen in the organism is identified by episodes of absence of breathing (apnea), purple coloration of the skin (cyanosis) or hypoxemia (established by measuring the oxygen level in the peripheral arterial blood) and has been strongly associated as a harmful factor in the evolution of patients with severe TBI. Diverse clinical studies have identified hypoxia at a prehospital level as one of the predictive elements strongly associated with the presence of neurological disability and mortality in these patients after being discharged. This has been associated with the physiological mechanisms that trigger so-called secondary brain injuries, especially the changes related to ischemia, necrosis and brain swelling. Advanced management of airways through orotracheal intubation is one of the fundamental principles when treating patients with severe TBI in emergency departments of low, medium and high level health centers. Observational
studies have been inconsistent in trying to identify if the use of this procedure in prehospital care (before arriving at health centers) reduces neurological disability and mortality in patients with severe TBI, or not. This is mainly due to heterogeneity in the management protocols, evaluation of heterogeneous populations and evaluations of monitoring being limited to the stay in hospital. All these studies have been made in environments different to Latin America. There has only been one controlled and randomized clinical study that compared prehospital orotracheal intubation with in-hospital orotracheal intubation in adult patients with severe TBI. It was published in 2010, and evaluated the results in terms of neurological disability and mortality in the 6 months following the injury in an Australian population. All the clinical studies published on the topic between 1990 and 2013 in English and Spanish were evaluated to determine the level of evidence presented by the studies, in order to conclude if prehospital orotracheal intubation reduces neurological disability and mortality in patients over 15 years old with severe TBI, compared with situations where it is carried out in the emergency departments of health centers.

**Summary of the evidence**

A total of 14 observational studies together with 1 randomized controlled clinical study were evaluated (See Annex 6). After reviewing these studies, the recommendation was based on the only randomized and controlled clinical study, in patients over 15 years old with severe TBI (Bernard 2010). This study randomized 312 patients to prehospital orotracheal intubation with a rapid sequence of medication, or to manual ventilation until the patient arrived at the hospital for orotracheal intubation in the emergency department. In this study, adequate training as part of training programs was considered to be at least 16 hours of theoretical-practical training in the rapid sequence of intubation, including at least 4 hours of theory, 8 hours of experience in intubation in operating theaters under the supervision of an anesthesiologist and at least 4 hours of evaluation in simulations. Mortality after 6 months was 33.8% in patients intubated before arriving at hospital and 38.7% for patients’ intubated in-hospital in the emergency department. The success rate of pre-hospital intubation was 97%. After six months, the percentage of patients with a favorable outcome (GOS 5–8) was 51% in the group intubated in the ambulance, compared with a favorable outcome (GOS 5-8) of 39% in the group that were intubated in-hospital. Upon analyzing the available literature, it was found that the great majority of
studies that supported this intervention were made in environments in which training of prehospital personnel has a suitable academic certification for carrying out the procedure, which is renewed periodically. For this reason, an additional search was made in order to look for evidence on the success rate in the procedure of intubation by paramedics and if there is any relationship between this and the level of experience of the person who performs the procedure.

The recommendation was made based on one randomized study, which compared the success rate of intubation made by paramedics in training with that of expert pre-hospital laryngoscopists (medics and paramedics) in a model of difficult intubation (Woollard 2008). The rate of intubation at the first attempt for paramedics in training was 0/23 (0%) and for expert laryngoscopists was 14/56 (25%). The esophageal intubation rate for paramedics in training was 15/23 (65%) and for expert laryngoscopists was 9/56 (16%). The failure rate for difficult intubation was 57.1% for expert laryngoscopists and 69.6% for paramedics in training, after 3 attempts.

From evidence to recommendation
During the meeting with the GDG it was considered that this is a strong recommendation in favor of intervention, because the balance between the desired results (improvement in disability and reduction in mortality after 6 months) versus the undesired (injury to airways, esophageal intubation and adverse reaction to medication during the procedure) is highly in favor of the first group. The group took into account the study of cost-effectiveness made in the economic section of this guide and discussed the aspects of availability of resources and safety of the intervention. For this reason, and taking into account the quality of the evidence, specific recommendations were established that are directed towards offering quality care with aspects that must be strengthened with evaluation of compliance by the respective organizations. This compliance must be evaluated specifically in aspects of training in protocols of rapid intubation and alternative methods of management of airways in the case that the intubation process fails. The development group discussed the importance of suggesting doses of medication adjusted to the average weight of the Colombian population, taking into account the medication used in the evaluated study.
Structural requirements
We consider that to bring about this recommendation, there is a need for appropriately trained personnel in the procedure of intubation with a rapid sequence of medication. The current programs of study in medicine and technology in prehospital care have specific modules for training in orotracheal intubation. Additionally, and taking into account the Colombian standards for habilitation of health care transport units, it is considered that the necessary resources to carry out the procedures are the following:

Basic Care Transport Unit
- **Personnel**: Technologist in PHC (Pre-hospital care) or professional technician in PHC or nursing assistant with certificate of training in the skill of basic life support.
- **Equipment**: Pulse oximeter, medicinal oxygen system.
- **Medication, medical devices or supplies**: self-inflatable bag-valve-mask device with oxygen tanks for adults, supraglottic airway devices in different sizes.

Unidad de Traslado Asistencial Medicalizado
- **Personnel**: Doctor, Nurse or Technologist in PHC, with certificate of at least 48h of training in advanced life support.
- **Equipment**: Pulse oximeter, medicinal oxygen system, portable mechanical ventilator, adult laryngoscope with 3 valves of different sizes, laryngeal masks of different sizes, intubation guide and capnograph.
- **Medication, medical devices or supplies**: Vials of midazolam (5mg or 15mg), vials of fentanyl (500μg or 1.000μg), vials of succinylcholine (100mg or 250mg), endotracheal tubes of different sizes.

The abovementioned items must be considered during the development of formats of clinical histories in transport and emergency services of any level of complexity.

Considerations regarding benefits and risks
It is considered that the benefit of prehospital orotracheal intubation in patients with compromised oxygenation associated with an intra-
cranial injury outweighs the risk associated with late intubation in the health center that initially manages the patient. The risks associated with a problem during the process of intubation with a rapid sequence of medication are equal in both situations (prehospital and in-hospital). These risks will be minimized if each unit has the recommended equipment and the suggested training process.

Considerations regarding values and preferences of patients
Patients and their caregivers show a clear preference for the opportunity to have access to advanced comprehensive care, which includes the fact that the personnel who carry out the procedures have a suitable level of training in order to perform the interventions that are required, as soon as possible after the injury. Therefore, there was no consideration that changes the recommendations.

Implications regarding resources
It is considered that the benefit of applying the recommendation is cost effective, considering that the cost of complications associated with cerebral hypoxia due to not receiving suitable treatment can be much greater than the cost that could result from the use of appropriate resources to carry out the procedure. It must be taken into account that this guide makes the first study of cost-effectiveness in Colombia for this specific question. The study clearly shows that intervention is cost-effective.

References
Flowchart for the process of inclusion in articles

References identified through searches of databases (n=95)
- Pubmed: 65
- Embase: 0
- Biosis: 10
- Scisearch: 11
- Medpilot: 3
- Cochrane: 2
- Tripdatabase: 4

References obtained manually (n=9)

All references obtained (n=104)

Duplicate References (n=6)

References included with title and abstract that were revised. (n=98)

Articles not related (n=88)

Revised Articles (n=10)

Excluded articles (n=9)
  Not adequately show the results: 2

Included articles (n=1)
Algorithm 2

Prehospital intubation (question 3)

Adult patient with severe TBI in ambulance

Evaluate systolic blood pressure (SBP) and age range

SBP<100 mmHg or age >60 years

Yes

If the patient has not been intubated (OTI), perform rapid sequence intubation. It is recommended that you use half of the conventional-dose of the induction drugs. *

Orotracheal intubation successful**

Yes

Continue transfer to emergency room (see Algorithm Question No. 6, Surgery time)

No

PSBP>100 mmHg or age <60 years

No

Provide 250 cc of normal saline

If the patient has not been intubated (OTI), perform rapid sequence intubation. It is recommended that you use the conventional-dose of the induction drugs. *

Continue ventilation system with a bag-valve-mask (BVM) along with oropharyngeal cannula

Pulse oximetry is higher than 90%

Yes

Pulse oximetry is less than 90%

No

Place laryngeal mask

*The recommended dosages to be used are the following:
- Fentanyl  Dose: 1 μg/Kg
- Midazolam  Dose: 0.1mg/Kg
- Succinylcholine  Dose: 1 mg/Kg

**In verified, tracheal intubation with pulse oximetry >90%. Orotracheal intubation in a prehospital setting, should be performed by skilled medical personnel or prehospital technologists (who have an adequate level of training). Technologists must carry out the procedure under direct or indirect supervision of a physician with experience in the management of prehospital and in-hospital emergencies.
Question 4

In adult patients with severe TBI, does the use of 7.5% hypertonic solutions for resuscitation in prehospital setting, compared with the use of isotonic resuscitation solutions, reduce neurological disability or mortality, evaluated at 6 months post-injury?

Recommendation

- It is recommended that adult patients with severe blunt TBI without hypotension can be treated at a prehospital level with 250ml of saline solution at 0.9%
  ✓ Strong recommendation in favor of intervention, moderate quality of evidence

- It is recommended that patients with penetrating TBI or with hypotension can be treated at a prehospital level with 250ml of saline solution at 0.9%.
  ✓ Good clinical practice.

Introduction

Severe TBI generates cellular responses that increase the likelihood of injury including ischemia associated with hypoxia and hypotension inducing more cell injury. It has been shown that ischemia and inflammation following head trauma start from the moment of injury (Gaetz 2004, Miller 1978). Early and timely control of physiological variables such as oxygenation and blood pressure has been associated with a decrease in mortality and disability in patients with severe TBI (Chestnut 1993, Chestnut 1995, Stocheti 1996). Prehospital treatment of patients with severe TBI has been a controversial topic because of the difficulty to perform appropriate studies in this type of scenario. There is significant variability in the type of solutions used in the prehospital environment and there are even discussions about the usefulness or otherwise of the use of resuscitation solutions during the initial care of these patients starting at the accident site (Sampalis 1997, Geeraerts 2007). In Colombia, there is great variability in prehospital
care and there are even cases of prolonged transportation of patients with severe TBI when they are from rural areas. There is currently a trend towards the use of hypertonic solutions in patients with severe TBI as these solutions generate a double effect as both a hyperosmolar solution for the reduction of ICP and due to the expansion effect of the intravascular space due to the high concentration of sodium in the space. For these reasons and because of the great variability that exists in the management of prehospital fluids in Colombia, it was considered important to compare the solution most used in our country, Normal Saline (NS) versus that suggested by the recent literature, Hypertonic Saline (HS).

Summary of the evidence
A total of 10 randomized trials on the use of prehospital resuscitation solutions in patients with severe TBI were found (See Annex 6). Only one study met the criteria for the PICO question by comparing saline (7.5%) with NS in adult patients with severe head trauma (Bulger 2010). This study randomized 1331 patients with severe TBI. Complete monitoring was performed on 1087 of them for the 6 months following discharge. Of these, 302 were included in the group receiving hypertonic saline and dextran, 293 were included in the group of hypertonic saline (7.5%) and 492 in the group receiving NS. The characteristics of the groups were similar, predominantly type II diffuse injuries and mass injuries. More than 58% of the patients in both groups were intubated in prehospital situations and the average transfer time was close to 50 minutes. In total, 650 milliliters of solution were administered in each of the groups. 40.8% of patients treated with hypertonic saline were transferred by air, compared to 37.4% of those treated with NS. The group receiving hypertonic saline, presented levels above 145 meq/l of sodium, a much higher percentage compared to the NS group; these levels remained high, especially in the first 12 hours. The groups had similar results in terms of mortality and severe disability. The group treated with hypertonic saline (7.5%) had a survival rate of 58.4% and the group treated with NS had a rate of 56.1%. Disability (GOS-E <4) for the hypertonic saline (7.5%) group was 50.1%, and in the NS group this was 47.4%.
From evidence to recommendation
During the meeting with the working group, it was considered that the balance of desired outcomes (improved survival and disability at 6 months) vs unwanted outcomes (increased mortality or disability at six months) is equal for the two interventions. Considering the aspect of the availability of hypertonic saline in Colombia (not found commercially) and risks that may occur during preparation (variation in concentrations, contamination of sterile solutions, biological accidents with needles, etc) it was considered important to establish a recommendation for normal saline, as this is available and does not require additional preparations or mixtures with other medications. The working group discussed the specific situation of patients with severe penetrating TBI or patients with hypotension and it was considered important to use the same recommendation as good clinical practice, since there are no studies that respond specifically to this type of patients, comparing normal saline with 7.5% hypertonic solution. Additionally, the only studies made in general trauma patients comparing normal saline (0.9%) and hypertonic solutions (7.5%) or in patients with severe TBI comparing hypertonic saline with Ringer Lactate solution, showed no differences between the used solutions.

Structural requirements
It is considered that to carry out this recommendation, no infrastructure is required in addition to that, which is already available within the Colombian system of social security in health.

Considerations on benefits and risks
It is believed that the benefit of implementing the recommendation does not imply any risk associated with the use of the solution, especially since the recommendation is for the use of a small volume (250ml), which is not associated with the risk of fluid overload and/or overhydration in patients.

Considerations on the values and preferences of patients
For this recommendation in particular, no values or preferences were expressed. The patients and their caregivers expressed a clear preference for the opportunity to have appropriate prehospital treatment immediately after the injury.
Implications on resources
It is considered that the benefit of applying the recommendation may be cost effective, given that the cost of an intracranial injury without appropriate treatment can be much greater than the cost of the use of a 250ml bolus of Normal Saline. It is important to bear in mind that there are no economic studies on the implications of this recommendation in Colombia.

References
Flowchart for the process of inclusion in articles

References identified through searches of databases (n=95)
- Pubmed: 5
- Embase: 33
- Biosis: 0
- Scisearch: 0
- Medpilot: 1
- Cochrane: 0
- Tripdatabase: 0

References obtained manually (n=10)

All references obtained (n=49)

Duplicate References (n=0)

References included with title and abstract that were revised (n=49)

Articles not related (n=39)

Revised Articles (n=10)

Excluded articles (n=9)
- Evaluate presentations not available in the country: 6
- Compared with other crystalloid different from that of the question: 3

Included articles (n=1)
Algorithm 3
Prehospital Fluids (question 4)

Adult Patient with severe TBI with intracranial hypertension (IHT) measured with ICP > 20 mmHg

- Refractory IHT >25 mmHg by more than 5 minutes
  - Yes: Continue sedation algorithm (see question no. 7, Sedation)
  - No: Provide a bolus of 2 cc/kg of hypertonic saline solution 7.5% or mannitol 20%

- SBP > 90 mmHg
  - Yes: Provide a bolus of 2 cc/kg of hypertonic saline solution 7.5%
  - No: Provide a second bolus of hypertonic saline solution 7.5% or mannitol 20%, 10 minutes after you have completed the first bolus. Do not use mannitol if SBP < 90 mmHg.

- Is ICP decreased?
  - Yes: Continue sedation
  - No: Consider hypothermia (see algorithm question No. 10), consider surgery for cerebral edema before 24 hours (see algorithm question No. 6)
**Question 5**

In adult patients with severe TBI and intracranial hypertension, does the use of hypertonic saline at 7.5%, compared with mannitol, as a hyperosmolar initial therapy reduce mortality at discharge?

**Recommendation**

- It is suggested that adult patients with severe TBI and refractory intracranial hypertension (ICP > 25 mmHg for more than 5 minutes, measured with an intracranial pressure measuring device) be treated with a bolus of 2 ml/kg of 7.5% hypertonic saline solution or mannitol at 20%.
  - Weak recommendation in favor of intervention, moderate quality of evidence.

- If the first dose is not effective in reducing ICP, a second bolus of 7.5% hypertonic saline solution or mannitol at 20% may be administered 10 minutes after finishing the first bolus.
  - Weak recommendation in favor of the intervention, moderate quality of evidence.

- It is considered that adult patients with severe TBI and non-refractory intracranial hypertension (20-25 mmHg, measured using an intracranial pressure device) requiring hyperosmolar therapy should be treated with a bolus of 2 cc/kg of 7.5% hypertonic saline solution or mannitol at 20%.
  - Good clinical practice

- It is considered that for the preparation of the 7.5% hypertonic saline solution, a mixture of (40%) 0.9% saline solution plus (60%) ampoules of sodium chloride should be used. To prepare 250cc of the solution, 100cc of normal saline solution and 15 ampoules of sodium chloride (20meq/10ml) would be mixed.
  - Good clinical practice

- It is considered that the use of mannitol at 20% should be performed only in normotensive patients with systolic blood pressure greater than 90 mmHg.
  - Good clinical practice
Introduction
In patients with severe TBI, between 60% and 70% of patients approximately have abnormalities in the tomography upon admission (concussion, intracerebral, extradural or subdural hematoma and/or signs of cerebral edema). A high percentage of these patients present intracranial hypertension associated with low perfusion of brain tissue. One of the medical therapies that have proved to be effective in reducing intracranial pressure (ICP) is the infusion of hyperosmolar solutions (osmotherapy). Two of the most commonly used solutions for osmotherapy are mannitol (20%) and hypertonic saline at various concentrations including 3%, 7.5% and 23.4% preparations. Therefore, there is variability in the decision of the solution to be infused and its concentration. Two of the most used solutions both in emergency and intensive care are mannitol and hypertonic saline (7.5%). Therefore, it is necessary to determine whether or not there is a difference in mortality associated with the use of one or another of the solutions.

Summary of the evidence
Six observational studies were analyzed, finding great variability in concentrations of the solutions used; the vast majority of these studies did not assess mortality but physiological changes in monitored parameter values including ICP. The study from Vialet (2003), besides being a randomized controlled study was the only one that precisely answered the PICO question by including only adult patients with severe TBI and comparing the two solutions at the concentrations stated in the question. Furthermore, it evaluated mortality and neurological disability as outcomes. In this study, two groups were randomized for treatment of refractory endocranial hypertension by 2 cc/kg hypertonic saline (7.5%) vs 2cc/kg of mannitol (20%). The group treated with hypertonic saline presented a better control of intracranial pressure and lower requirement for drainage of cerebrospinal fluid (CSF) through a ventriculostomy catheter. Mortality evaluated at 3 months after hospital discharge showed no significant difference between the two groups. In the group treated with hypertonic saline (7.5%) it was 40%, and for the group treated with mannitol (20%) it was 50%. There were no differences in electrolyte changes or hemodynamic changes either.
From evidence to recommendation
In the discussion of the working group, the quality of the evidence presented was confirmed and it was considered important to make a suggestion for how to prepare hypertonic saline (7.5%) due to heterogeneity in its preparation and the scarce availability of its commercial presentation in Colombia. Emphasis was placed on the appropriate hemodynamic status of patient (no hypotension) prior to use of mannitol as hyper-osmolar therapy. Both interventions were considered low-cost.

Structural requirements
It is considered that to carry out this recommendation, no infrastructure is required in addition to that already available within the Colombian system of social security in health. Although there is no commercial version of 7.5% saline, it can be prepared in intensive care units, mixing a solution of 60% normal saline and 40% sodium chloride.

Considerations on benefits and risks
It is considered that the benefit of applying the recommendation to either of the two substances outweighs the risk of not correcting an episode of refractory intracranial hypertension, which may be associated with higher mortality and disability rates.

Considerations on the values and preferences of patients
For this recommendation in particular, no value or preference was expressed.

Implications on resources
It is considered that the benefit of applying the recommendation may be cost effective, given that the cost of the complications associated with refractory intracranial hypertension without appropriate treatment (brain herniation, cerebral infarction, brain death), can be much greater than the cost that may arise from the use of the above solutions. It is important to bear in mind that there are no economic studies on the implications of this recommendation in Colombia.
References


Flowchart for the process of inclusion of articles
Question 6a

In adult patients with severe TBI and acute subdural hematoma with surgical indication, does early drainage surgery (within 4 hours), compared with late surgery (after 4 hours), reduce mortality at discharge?

Recommendation

- It is recommended that surgical treatment be performed in the first 4 hours post-trauma in patients with severe head trauma with acute subdural hematoma with surgical indication.

✓ Recommendation by strong consensus in favor of the intervention.

Introduction

Acute subdural hematoma is one of the most critical injuries associated with high mortality in patients with severe TBI. It often requires surgical intervention and mortality rates are highly variable but may be as high as 70% depending on the institution where patients arrive. Time-to-surgery has been proposed as one of the prognostic factors given that the presence of this lesion is often associated with the mass effect, which generates a significant midline shift and compression of vital structures such as the brainstem. There are currently no treatment guidelines that establish a specific time of intervention for these patients in Colombia. Therefore, there is great variability in the time of surgery for patients with severe TBI having a subdural hematoma upon admission and hence the need to respond to this question.

Summary of the evidence

For this question, eight observational studies were found, none of which responded to the PICO question. Therefore, it was necessary to use a formal consensus of experts. Studies identified in the search, but which did not meet all the criteria of the PICO question were sent to all participants. They later attended a two-hour face-to-face meeting. The group was composed of experts working in prehospital care, emergency care, intensive care and neurosurgery services in different regions of the country, both in public and private institutions (Table 10).
A presentation on the results of the literature review was conducted. For this group, the question raised was: Do you think that surgery on a patient with acute subdural hematoma and surgical indication should be performed before or after 4 hours from the time of injury?. The time criteria of 4 hours was established in accordance with the studies reviewed concerning the subject, but that included mixed populations (pediatric and adult and/or moderate and severe trauma), and because of that reason they could not be taken into account for the construction of evidence tables for PICO criteria. Subsequently, a discussion space was proposed, in which the experts presented their views on the question under discussion. The members of the working group acted as moderators and clarified doubts about the interpretation and analysis of the various studies previously sent. There was one round of voting with 14 experts, in which the result was unanimous in favor of early intervention (first 4 hours) after the injury.
From evidence to recommendation
It was considered important that this surgical procedure be performed as recommended within the limit of four hours, as this has been considered in many observational studies, and their correlation with outcome shows a clear trend between early intervention and survival. It was also important to consider the opinions given by the patients and their caregivers, who consider early surgery crucial if there are indications for intervention. The most common indications for surgery include: acute subdural hematoma greater than 10mm thick, subdural hematoma causing a midline shift of more than 5 mm, and an acute subdural hematoma causing obliteration of basal cisterns.

Structural requirements
It is considered that to carry out this recommendation, no infrastructure is required in addition to that, which is already available within the Colombian system of social security in health. A neurosurgeon must be available to determine surgical criteria when the patient arrives at the emergency department.

Considerations on benefits and risks
It is considered that the benefit of implementing the recommendation of early intervention does not imply risks for the patient, and decreases their risk of disability and mortality associated with the injury.

Considerations on the values and preferences of patients
For this recommendation in particular, patients and their caregivers emphasized a preference for early intervention, perceiving it as a more effective intervention for improving chances of a better outcome.

Implications on resources
It is considered that the benefit of implementing the recommendation may be cost effective, given that the cost of the complications associated with late intervention (brain herniation, cerebral infarction, brain death, etc.), can be much greater than the cost which might be caused by early surgical intervention. It is important to bear in mind that there are no economic studies on the implications of this recommendation in Colombia.
Flowchart for the process of inclusion of articles

References identified through searches of databases
(n=319)

- Pubmed: 147
- Embase: 127
- Biosis: 1
- Scisearch: 2
- Medpilot: 20
- Cochrane: 21
- Tripdatabase: 1

References obtained manually (n=8)

All references obtained (n=327)

Duplicate References (n=23)

References included with title and abstract that were revised (n=304)

Articles not related (n=296)

Revised Articles (n=8)

Excluded articles (n=8)

Did not respond exactly the question: 8

Included articles (n=0)

The question was answered by expert consensus
**Algorithm 4**

*Time-to-surgery (question 6)*

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**Adult Patient with severe TBI intubated in the emergency room.**

**CT findings at Emergency Room**

- It has a subdural hematoma with surgical indication?
  - **Yes**
    - Surgical management should be performed in the first 4 hours post-trauma
  - **No**
    - The patient should be taken to surgery immediately

- It has an epidural hematoma with surgical indication?
  - **Yes**
    - The patient should be taken to surgery in the first 24 hours
  - **No**
    - Transfer to ICU \(^1\) (see algorithm No. 7, Sedation)

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*Criteria of indication of surgery for subdural hematoma (SH) in adult patients with severe TBI:*
- SH >10 mm of thickness measured at its larger diameter
- SH that produces mid line shift > 5 mm
- SH that produce compression of the basal cisterns (perimesencephalic cisterns)

*Criteria of indication of surgery for epidural hematoma (EH) in adult patients with severe TBI:*
- EH volume greater than 30 cc
- EH that produces mid line shift >5 mm

*Criteria of indication of surgery for cerebral edema in adult patients with severe TBI:*
- Cerebral edema with mid line shift > 5 mm
- Cerebral edema that produces compression of the basal cisterns (perimesencephalic cisterns)

\(^1\) It is considered that the patients with brain contusions (intracerebral hemorrhage) must be brought to surgery, if they meet the same criteria for surgical indications from cerebral edema or if the volume of the hemorrhage is bigger than 50 cc.
Question 6b

In adult patients with severe TBI, and an epidural hematoma with surgical indication, does early drainage surgery (within 4 hours), compared with late surgery (after 4 hours), reduce mortality at discharge?

Recommendation

- It is recommended that patients with severe TBI and an epidural hematoma with surgical indication for drainage be taken to surgery immediately.

✓ Recommendation by strong consensus in favor of the intervention.

Introduction

It is considered that an epidural hematoma may be present in up to 30% of patients with severe TBI. In these patients, the hematoma is associated in a high percentage of cases with the mass effect, midline shift and compression of vital structures such as the brainstem. Currently in Colombia there are no management guidelines that establish a specific time of intervention for these patients.

Summary of the evidence

For the answer to this question, five studies related to surgical management of acute epidural hematoma were reviewed. None responded exactly to the PICO question. Therefore, it was necessary to use a formal consensus of experts. Studies identified in the search, but which did not meet all the criteria of the PICO question were sent to all participants. Subsequently, they attended a face-to-face meeting lasting two hours. The group was composed of experts working in prehospital care, emergency departments, intensive care and neurosurgery services in different regions of the country, both in public and private institutions (Table 11).
A presentation was made with the results of the literature review. For this group, the question raised was: Do you think that surgery on a patient with an epidural hematoma and surgical indication should be performed immediately after the moment of trauma? The “immediate” time criteria was established according to the revised studies concerning the subject, but which included mixed populations (children and adults and/or moderate to severe trauma), and because of that reason could not be considered for the building of evidence tables for PICO criteria.

Subsequently, a discussion space was created, in which the experts presented their views on the question under discussion. Members of the working group acted as moderators and clarified doubts about the interpretation and analysis of the various studies previously sent. There was one round of voting with 14 experts, in which the result was unanimous in favor of immediate action after injury, once the patient enters the emergency room.
From evidence to recommendation
It was considered important that this surgical procedure be performed as recommended, since in many observational studies a clear trend between early intervention and survival is evident. This was also in line with the views of patients and their caregivers, who consider early surgery crucial if there are indications for intervention. The most frequent indications for surgery include: an epidural hematoma greater than 30cc, an epidural hematoma that causes a midline shift of more than 5 mm, and an epidural hematoma causing obliteration of basal cisterns.

Structural requirements
It is considered that to carry out this recommendation, no infrastructure is required in addition to that, which is already available within the Colombian system of social security in health. A neurosurgeon must be available to determine the criteria for surgery when the patient arrives at the emergency department.

Considerations on benefits and risks
It is considered that the benefit of applying the recommendation of immediate action does not involve risks to patients, and decreases disability and mortality rates associated with the injury.

Considerations on the values and preferences of patients
For this recommendation in particular, patients and their caregivers emphasized a preference for early intervention, perceiving it as more effective at improving chances of a better outcome.

Implications on resources
It is considered that the benefit of implementing the recommendation may be cost effective, given that the cost of the complications associated with late intervention (brain herniation, cerebral infarction, brain death, etc.), can be much greater than the cost which might arise from early surgical intervention. It is imperative to keep in mind that there are no economic studies on the implications of this recommendation in Colombia.
Flowchart for the process of inclusion in articles

References identified through searches of databases (n=323)
- Pubmed: 147
- Embase: 127
- Biosis: 1
- Scisearch: 2
- Medpilot: 20
- Cochrane: 21
- Tripdatabase: 5

References obtained manually (n=5)

All references obtained (n=328)

Duplicate References (n=23)

References included with title and abstract that were revised (n=305)

Articles not related (n=300)

Revised Articles (n=5)

Excluded articles (n=5)
- Did not respond exactly the question: 8

Included articles (n=0)
- The question was answered by expert consensus
Algorithm 4
Time-to-surgery (question 6)

Adult Patient with severe TBI intubated in the emergency room.

CT findings at Emergency Room

It has a subdural hematoma with surgical indication? *

Surgical management should be performed in the first 4 hours post-trauma

Yes

No

The patient should be taken to surgery immediately

It has an epidural hematoma with surgical indication? **

Yes

The patient should be taken to surgery in the first 24 hours

No

It has a cerebral edema with surgical indication? ***

No

Transfer to ICU (see algorithm No. 7, Sedation)

*Criteria of indication of surgery for subdural hematoma (SH) in adult patients with severe TBI:
- SH >10 mm of thickness measured at its larger diameter
- SH that produces mid line shift > 5 mm
- SH that produce compression of the basal cisterns (perimesencephalic cisterns)

**Criteria of indication of surgery for epidural hematoma (EH) in adult patients with severe TBI:
- EH volume greater than 30 cc
- EH that produces mid line shift >5 mm

***Criteria of indication of surgery for cerebral edema in adult patients with severe TBI:
- Cerebral edema with mid line shift > 5 mm
- Cerebral edema that produces compression of the basal cisterns (perimesencephalic cisterns)

It is considered that the patients with brain contusions (intracerebral hemorrhage) must be brought to surgery, if they meet the same criteria for surgical indications from cerebral edema or if the volume of the hemorrhage is bigger than 50 cc
Question 6c

In adult patients with severe TBI and surgical indication for cerebral edema, does early decompression craniectomy (within 24 hours), compared with late craniectomy (after 24 hours), reduce mortality at discharge?

Recommendation

- It is suggested that patients with severe TBI and surgical indication for cerebral edema be taken to surgery within 24 hours.
- Weak recommendation in favor of the intervention, low quality of evidence.

Introduction

In patients with severe TBI, approximately 60 to 70% of cases present abnormalities in tomography at admission (concussion, intracerebral, extradural or subdural hematoma and/or signs of cerebral edema). Approximately two thirds of these patients with imaging abnormalities present intracranial hypertension unresponsive to medical treatment (refractory intracranial hypertension) (Narayan 1982, Little 1998, Wardlaw 2002). The sustained elevated ICP is clearly correlated with increased mortality and increased functional sequelae after severe TBI (Vik 2008). Cranial decompression is an effective procedure to reduce ICP associated with severe TBI. The time to perform this surgery has been proposed as one of the predictors, but currently there are no management guidelines that allow a specific time for this intervention to be established. Therefore, there is variability in the time elapsed from the moment of trauma to decompression surgery in patients with severe TBI who have indications for the procedure. This is why there is a need to answer this question.

Summary of the evidence

In total, five observational studies were analyzed. The table of evidence was constructed for the sole observational study that responded exactly to the PICO question in terms of the population included and the measured results (Cianchi 2012). In this study, 186 patients with
Severe TBI admitted to the ICU of a tertiary hospital were analyzed. The patients were divided in 2 groups defined as early decompression (within 24 hours) and late (after 24 hours). There was also a control group of patients with intracranial hypertension who were managed medically. 41 patients were included in the first group, 21 in the second and 124 in the control group. These patients were analyzed using the GOS scale at 6 months post-injury finding a mortality rate of 48.8% in early surgery patients and 42.2% of patients with late surgery. Disability at 6 months showed an average of 3.3 on the GOS in the early group and 3.0 in the late intervention group. This describes more marked disability in the late intervention group.

**From evidence to recommendation**

During the discussion with the working group, it was decided to give a weak recommendation for intervention because the balance between desired outcomes (reduced disability and increased survival at 6 months) vs unwanted (increased disability and higher mortality at 6 months) is low in favor of the first outcome. It was considered important, taking into account aspects of patient safety, that this surgical procedure should be performed as recommended in the evidence and that the limit of 24 hours should be considered the maximum time allowed to perform the procedure. The most widely used surgical criteria, which were found to be appropriate, include: cerebral edema with midline shift greater than 5mm, and cerebral edema that causes compression of the basal cisterns.

**Structural requirements**

It is considered that to carry out this recommendation, no infrastructure is required in addition to that, which is already available within the Colombian system of social security in health. A neurosurgeon must be available to determine the criteria for surgery when the patient arrives at the emergency department.

**Considerations on benefits and risks**

It is considered that the benefit of applying the recommendation of immediate action does not involve risks to patients, and decreases disability and mortality rates associated with the injury.
Considerations on the values and preferences of patients

For this recommendation in particular, patients and their caregivers emphasized a preference for early intervention, perceiving it as more effective at improving chances of a better outcome.

Implications on resources

It is considered that the benefit of applying the recommendation may be cost effective, given that the cost of the complications associated with late intervention (brain herniation, cerebral infarction, brain death, etc.), can be much greater than the cost which might arise from early surgical intervention. It is imperative to bear in mind that there are no economic studies on the implications of this recommendation in Colombia.

References

Flowchart for the process of inclusion in articles

References identified through searches of databases (n=325)
- Pubmed: 147
- Embase: 127
- Biosis: 1
- Scisearch: 2
- Medpilot: 20
- Cochrane: 21
- Tripdatabase: 7

References obtained manually (n=5)

All references obtained (n=330)

Duplicate References (n=23)

References included with title and abstract that were revised (n=307)

Articles not related (n=302)

Revised Articles (n=5)

Excluded articles (n=4)
Did not respond exactly the question: 8

Included articles (n=1)
Algorithm 4
Time-to-surgery (question 6)

Adult Patient with severe TBI intubated in the emergency room.

CT findings at Emergency Room

---

Surgical management should be performed in the first 4 hours post-trauma

It has a subdural hematoma with surgical indication? *

Yes

The patient should be taken to surgery immediately

No

It has an epidural hematoma with surgical indication? **

Yes

The patient should be taken to surgery in the first 24 hours

No

It has a cerebral edema with surgical indication? ***

Yes

Transfer to ICU ³ (see algorithm No. 7, Sedation)

No

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*Criteria of indication of surgery for subdural hematoma (SH) in adult patients with severe TBI:
- SH >10 mm of thickness measured at its larger diameter
- SH that produces mid line shift > 5 mm
- SH that produce compression of the basal cisterns (perimesencephalic cisterns)

**Criteria of indication of surgery for epidural hematoma (EH) in adult patients with severe TBI:
- EH volume greater than 30 cc
- EH that produces mid line shift >5 mm

***Criteria of indication of surgery for cerebral edema in adult patients with severe TBI:
- Cerebral edema with mid line shift > 5 mm
- Cerebral edema that produces compression of the basal cisterns (perimesencephalic cisterns)

³ It is considered that the patients with brain contusions (intracerebral hemorrhage) must be brought to surgery, if they meet the same criteria for surgical indications from cerebral edema or if the volume of the hemorrhage is bigger than 50 cc
**Question 7**

In adult patients with severe TBI being treated in an ICU, does sedation with propofol, compared to sedation using Midazolam, reduce neurological disability or mortality, assessed at 3 months post-injury?

**Recommendation**

- It is suggested that adult patients with severe TBI be sedated during their stay in the ICU using midazolam. Doses of 0.1-0.3 mg/kg/h are suggested.¹
  - Weak recommendation in favor of the intervention, moderate quality of evidence

- As a second choice after midazolam, propofol 1% can be used at a dose of 1.5 to 5 mg/kg/h.¹
  - Weak recommendation in favor of the intervention, moderate quality of evidence

- It is suggested that a triglyceride measurement be performed on patients sedated with propofol 1% within the first 24 hours. If the initial sample of triglycerides is lower than 350 mg/dl, periodic checks should be performed every 72 hours. If the value is greater than 350 mg/dl, repeat the sample within 24 hours. If the second sample is also above 350 mg/dl, treatment should be discontinued immediately. Patients should be closely monitored for the possible occurrence of propofol infusion syndrome (hyperkalemia, metabolic acidosis, cardiac arrhythmia, cardiovascular collapse and multi-organ failure).
  - Weak recommendation in favor of the intervention, moderate quality of evidence

- Patients should be closely monitored for the possible occurrence of propofol infusion syndrome (hyperkalemia, metabolic acidosis, cardiac arrhythmia, cardiovascular collapse and multi-organ failure).
  - Good clinical practice.

¹ The use of the Richmond Agitation-Sedation Scale (RASS) for the evaluation and control of sedation is suggested because it is the most widely used scale.
Introduction
Patients with severe TBI typically require sedative regimes for acute treatment with the aim of decreasing cerebral metabolic consumption, preventing episodes of agitation during mechanical ventilation and also as an anxiolytic effect during intensive care stay. Decreased intracranial pressure and improvement of cerebral perfusion pressure have been reported as beneficial effects of the use of these agents but some adverse effects, including hypotension and metabolic alterations, have also been reported. Different drugs have been used in these patients but currently there is significant variability in the protocols and recommendations established in intensive care units. In Colombia, two of the most commonly used drugs are midazolam and propofol, which have pharmacodynamic and pharmacokinetic properties that produce an appropriate response in the management of these patients. In Colombia benzodiazepines, and especially midazolam, are highly used due to their availability and cost. Internationally, it has been suggested that propofol is a more effective sedative and that it produces fewer adverse effects in patients with TBI. It is therefore necessary to determine whether there is a difference in mortality and neurologic disability depending on which sedative is used.

Summary of the evidence
A total of three randomized controlled trials were evaluated (see annex 6). One of them (Ghori 2007) met the criteria of population, intervention and results formulated in the PICO question, so the table of evidence was constructed based on this study. The study randomized 28 adult patients with severe TBI, of them, 15 received midazolam and 13 received propofol. This study found no differences between the use of midazolam or propofol as sedatives in the treatment of patients with severe TBI from the point of view of the neurological outcome, measured with the GOS at 3 months after hospital discharge. In the group of Midazolam, there was an outcome of GOS 4-5 (good neurological outcome) in 53.3% of cases, while for the Propofol group this was 53.8%. The study also analyzed plasma concentrations of neurological injury markers (S100 protein and nitric oxide) in the first 5 days of hospitalization in the ICU and likewise there were no differences in the levels of these markers when comparing the two sedatives. Since the use of propofol has been associated with alterations in lipid metabolism, it was considered important to evaluate studies comparing metabolic complications associated with the use of the two drugs.
Two randomized controlled clinical studies (Sanchez-Izquierdo 1998; Sandiumengue 2000) on populations of clinically ill trauma patients were reviewed. No such studies were found from populations specifically with severe TBI. The study by Sanchez-Izquierdo was used for the table of evidence, as it included the analysis of a subpopulation of patients with severe TBI. This study compared the use of propofol 1% with midazolam in 150 patients who were divided into three groups with an average of 30% of patients with TBI in each group. The group of patients treated with propofol showed an increase in triglyceride levels, especially in patients treated for more than 72 hours, and greater therapeutic failure associated to this cause (therapeutic failure was defined as being when doses higher than 6 mg/kg/h were required or if triglyceride levels increased above 350 mg/dL on two consecutive measurements within 24 hours or if there was one measurement greater than 500 mg/dL).

**From evidence to recommendation**

During the discussion with the working group, the grading of the quality of evidence was confirmed. Both proposals for intervention were considered, considering them inexpensive, and furthermore there was no discussion regarding availability in the domestic environment. The most discussed aspects were regarding safety in the use of Propofol, as the evidence obtained in the analysis of studies of metabolic complications when comparing the two drugs (in which hypertriglyceridemia was a cause for stopping use of the medication) showed a therapeutic failure of propofol, after which another sedative was required to continue treating patients. The group of experts also discussed the implications of propofol infusion syndrome, associated with hyperkalemia, arrhythmia and cardiovascular collapse, which, although not analyzed in the reviewed studies, has been described and is considered important by the group of experts. The last two points were taken into account when making the recommendation, in which the working group considered Midazolam as a first option as it is not associated with altered triglyceride levels or a risk of cardiovascular alterations induced by its infusion. The group also considered it important to use a scale for assessing the depth of sedation. This scale is the Richmond Agitation Sedation Scale, which is the scale that is most widely used in a standardized way for this purpose.
Structural requirements
It is considered that to carry out this recommendation, no infrastructure is required in addition to that, which is already available within the Colombian system of social security in health. Staff trained in the use of the Richmond Agitation Sedation Scale must be available to evaluate depth of sedation.

Considerations on benefits and risks
It is considered that the benefit of applying the recommendation on the use of sedatives outweighs the risk caused by their adverse effects. Special precaution must be taken with monitoring of the adverse effects of propofol, given that the presence of hyperkalemia can be associated with cardiac complications.

Considerations on the values and preferences of patients
For this recommendation in particular, patients and their caregivers did not state any preference that would modify the recommendation.

Implications on resources
It is considered that the benefit of applying the recommendation may be cost effective, given that the cost of the complications associated with not using sedatives in patients with brain injuries during the acute treatment of intracranial hypertension can be much greater than the cost that might arise from their use. It is important to have in mind that there are no economic studies on the implications of this recommendation in Colombia.

References
3. Sandiumenge CA, Sanchez-Izquierdo, RJA, Vazquez DT, Borges MS, Peinado RJ, AtedLE.Midazolam and 2% propofol in long-term

**Flowchart for the process of inclusion of articles**

- **References identified through searches of databases** (n=226)
  - Pubmed: 29
  - Embase: 171
  - Biosis: 3
  - Scisearch: 5
  - Medpilot: 4
  - Cochrane: 10
  - Tripdatabase: 4

- **References obtained manually** (n=3)

- **All references obtained** (n=229)

- **Duplicate References** (n=13)

- **References included with title and abstract that were revised** (n=216)

- **Articles not related** (n=213)

- **Revised Articles** (n=3)

- **Excluded articles** (n=2)
  - Systematic review that includes multiple types of interventions: 1
  - Normative review: 1
  - Review of clinical studies included multiple agents of sedation and clinical changes, but not in mortality: 1

- **Included articles** (n=1)
**Algorithm 5**  
**Sedation (question 7)**

**Adult Patient with severe TBI in ICU**

Start sedation with midazolam dose of 0.1 - 0.3 mg/kg/h or propofol 1% at dose of 1.5 to 5 mg/kg/h

In the event that management has been started with propofol perform measurement of triglycerides (TGC) in the first 24 hours

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**TGC > 350 mg/dl**

- **Yes**
  - Repeat sample before 24 hours

- **No**
  - Discard propofol and start midazolam

**Perform control of TGC in 72 hours**

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**TGC > 350 mg/dl**

- **Yes**
  - Continue ICU management (see algorithm question No. 9, Monitoring of ICP)

- **No**
  - Discard propofol and start midazolam
Question 8

In adult patients with severe TBI treated in an ICU, does thrombo-prophylaxis with low molecular weight heparin (LMWH), compared with thrombo-prophylaxis with unfractionated heparin, reduce the presence of thrombotic events and mortality at discharge?

Recommendation

- It is recommended that adult patients with severe TBI receive antithrombotic prophylaxis with low molecular weight heparin (enoxaparin). The suggested dose is 30mg/SC/day.
  ✔ Weak recommendation for intervention, low quality of evidence.

- The recommendation is to start antithrombotic therapy as soon as possible; as long as the patient is not receiving transfusions, is stable in the neurological examination (no reduction in GCS) and that the CT scan shows evidence that the bleeding is controlled (no expansion in the area of bleeding).
  ✔ Weak recommendation for intervention, low quality of evidence.

- Start pneumatic compression stockings in patients with severe TBI immediately after admission to the ICU.
  ✔ Good clinical practice.

Introduction

Deep vein thrombosis is a clinical picture particularly associated with patients who have a prolonged stay in an ICU. Patients with severe TBI are generally treated in these units for long periods of time. The association between severe TBI and deep vein thrombosis has been reported on different occasions and can reach figures as high as 50% of the patients, including other complications such as the formation of a pulmonary embolus (Geerts 1994). The pulmonary embolisms, including smaller ones, are associated with important events of hypoxia and desaturation, which have been clearly associated with increased early mortality in patients with severe TBI (Chesnut 1993). The use of different strategies to prevent thrombotic events in these patients has been proposed. Two of the most commonly used methods in Colombia are thromboprophylaxis with Low Molecular Weight Heparins (LMWH) and thromboprophylaxis with unfractionated heparin. Complications
such as intracerebral bleeding associated with the treatment have been described in both interventions. There is no consensus on the use of these drugs and therefore there is significant variability. Therefore there is a need to determine whether in patients with severe TBI, thromboprophylaxis with low molecular weight heparin versus unfractionated heparin reduces the occurrence of thrombotic events and mortality.

**Summary of the evidence**
An observational study (Minshall 2011) of 386 patients with severe TBI, determined by a head abbreviated injury scale score > 3, analyzed and compared 158 patients treated with low molecular weight heparin with 171 patients treated with unfractionated heparin. It was the only study that met the inclusion criteria of the PICO question. The dose of enoxaparin used was 30 mg subcutaneous twice daily and the dose of low molecular weight heparin was 5000 units subcutaneously three times a day. The mean time for starting therapy was 47 hours in patients with enoxaparin and 54 hours in patients receiving heparin. Mortality and thrombotic complications were higher in the group of unfractionated heparin, with a mortality assessed at discharge of 15.8% in this group, compared with a mortality of 5.1% in the group of low molecular weight heparin. Deep vein thrombosis occurred in 1.2% of the unfractionated heparin group and 0.6% in the group of low molecular weight heparin. The presence of pulmonary thromboembolism was 4.1% for the UFH group and 0% in the group receiving LMWH. Similarly, progression of intracerebral hemorrhage was greater in the second group.

**From evidence to recommendation**
In the group discussion, it was felt that there should be a weak recommendation to support the use of low molecular weight heparin (enoxaparin) because the balance between desired outcomes (lower mortality and fewer thrombotic and thromboembolic events) vs unwanted (progression of intracerebral bleeding) is high in favor of enoxaparin but the quality of evidence is low. There was agreement on the availability in our environment of the medication evaluated in the study. It was insisted that aspects related to safety (time of starting therapy and absence of active bleeding) were included and the group of experts considered it important to suggest a lower dose than that used in the study (30mg/24h vs 60mg /24h), taking into account that the
average weight of the North American population is higher than that of the Colombian population.

**Structural requirements**

It is considered that to carry out this recommendation, no infrastructure is required in addition to that, which is already available within the Colombian system of social security in health.

**Considerations on benefits and risks**

It is considered that the benefit of implementing the recommendation on the use of low molecular weight heparin outweighs the risk caused by their adverse effects. It is important to consider the criteria for the recommendation of starting time, especially after taking a control scan of the head.

**Considerations on the values and preferences of patients**

For this recommendation in particular, patients and their caregivers did not state any preference that would modify the recommendation.

**Implications on resources**

It is considered that the benefit of applying the recommendation may be cost effective, given that the cost of the complications associated with not using thromboprophylaxis in patients with brain injuries can be much greater than the cost that might arise from their use. It is important to keep in mind that in Colombia there are no economic studies on the implications of this recommendation.

**References**

Flowchart for the process of inclusion in articles

References identified through searches of databases (n=190)
- Pubmed: 63
- Embase: 86
- Biosis: 4
- Scisearch: 6
- Medpilot: 5
- Cochrane: 24
- Tripdatabase: 2

References obtained manually (n=6)

All references obtained (n=196)

Duplicate References (n=30)

References included with title and abstract that were revised (n=166)

Articles not related (n=160)

Revised Articles (n=6)

Excluded articles (n=5)

Included articles (n=1)

Not compared measurement of start times of thromboprophylaxis, and the outcome did not correspond to the question PICO: 5
Algorithm 6
Antithrombotic prophylaxis (question 8)

Adult Patient with severe TBI in ICU

The patient meets the following criteria: - is not receiving transfusions; - is stable in the neurologic examination (without deterioration in the Glasgow Coma Scale); - In the control CT, there is evidence that the bleeding is controlled (there is not increase in the size of the bleeding)

Yes

Start antithrombotic prophylaxis with low molecular weight heparin (enoxaparin). The suggested dose is 30 mg/SC/day

No

Start with pneumatic compression stockings

Continue ICU management (see algorithm question No. 7, Sedation and algorithm question No. 9, Monitoring of ICP)
Question 9

In adult patients with severe TBI being treated in an ICU, does guided therapy with monitoring of intracranial pressure (ICP), compared with treatment without ICP monitoring, reduce mortality at discharge?

Recommendation

- It is suggested that adult patients with severe TBI need to be monitored with intracranial pressure measurement devices when they meet the following criteria: Glasgow Coma Scale greater than or equal to 3 and less than or equal to 8 after resuscitation and an abnormal CT (hematoma, contusion, edema, herniation or compression of basal cisterns).
  - Weak recommendation in favor of intervention, very low quality of evidence.

- It is suggested that treatment of intracranial hypertension be initiated when the value measured in the patient is greater than 20mmHg in a single measurement.
  - Weak recommendation in favor of intervention, Very low quality of evidence.

Introduction

After severe TBI, patients can suffer alterations that lead to increases in ICP. These increases may be due to accumulation of blood in the epidural or subdural space, at intracerebral level and/or due to inflammation of the brain tissue. This increased pressure may be temporarily offset by the mobilization of cerebrospinal fluid from the cranial component to the spinal space or by decreasing the volume of intracerebral venous blood. When these mechanisms are exhausted, internal displacement of brain tissue (cerebral herniation or cerebellar) begins. This may cause death due to the compression of critical structures, especially in the brain stem. The increase in ICP occurs in the first hours and its duration may vary depending on the type of injury that
is causing it. Therefore, in patients with severe TBI, monitoring of ICP is considered an important tool in the acute care of patients. Several studies that have attempted to examine the relationship between the monitoring of ICP and functional outcome in patients have presented inconsistent results. A great majority of these studies were observational and the few clinical studies have biases that lower methodological quality. For this reason, it was considered important to perform this question for clinical practice guidelines in Colombia.

**Summary of the evidence**

A total of 11 studies were analyzed to answer the question, of which 10 were observational (Marmarou 1991, Lane 2000, Stiefel 2005, Balestreri 2006, Mauritz 2008, Farahvar 2012, Barmparas 2012, Thompson 2008, Shafi 2008 and Alali 2007) and one was a randomized clinical study (Chesnut, 2012). The latter study was not included due to having a population below the stated range for this guideline (+15). The 2 studies selected to answer the question of the guide, despite being observational studies, strictly met the criteria of population, intervention and outcomes (mortality) established in the PICO question. The first study (Shafi 2008) analyzed 1,646 patients over 20 years old with severe TBI of whom 708 received ICP monitoring and 938 did not. The two groups were compared and it was found that there was improved survival in the group of patients that was not monitored. Mortality in the group whose ICP was monitored was 27.7%, and mortality in the non-monitored group was 11.9%. However, the group of monitored patients had a higher abbreviated injury scale score, having suffered more severe head injuries, which can clearly influence the outcome. In the second study (Alali 2007) 10,628 adult patients in 155 trauma centers in the United States and Canada were analyzed. It was found that the institutions that monitored ICP had lower mortality rates at hospital discharge. A total of 1,874 patients were monitored and 8,754 were treated without monitoring. In this study, ICP monitoring was associated with lower mortality. Mortality in the monitored group of patients was 32% and mortality in the group of unmonitored patients was 36.2%.
From evidence to recommendation
The working group decided to give a weak recommendation for intervention, taking into account that the balance between desired outcomes (reduction in mortality at discharge) versus unwanted results (intracerebral hemorrhage or infection of the central nervous system, during the procedure) was small in favor of the first. Additionally, confidence in the magnitude of the estimated effect of the intervention on the important outcome (survival) is also low. Although both studies showed different results, the group discussed the heterogeneity in practice and safety aspects, especially post-insertion treatment in the ICU. The importance of understanding the monitoring process as a marker of treatment intensity was discussed, because this monitoring integrates clinical monitoring and imaging with additional physiological data, enabling more aggressive and early medical or surgical interventions. Findings from CT scans that should be taken into account as indicators for ICP monitoring, were added to the recommendation.

Structural requirements
It is considered that to carry out this recommendation, no infrastructure is required in addition to that, which is already available within the Colombian system of social security in health. Current standards for the provision of intensive care units establish what is necessary for the monitoring of invasive pressure, and intracranial pressure monitoring is established as one of the priority processes for intensive care units for adults. This measurement is usually performed in specialized centers that are referral centers for lower-level institutions. Given that care centers with emphasis on trauma are centers of high specialization (see recommendation question 2), the necessary resources for ICP monitoring (including equipment, devices, supplies and trained human talent for the measurement and interpretation of monitoring data) must be available at these centers to provide comprehensive management of adult patients with severe TBI.

Considerations on benefits and risks
It is considered that the benefit of implementing ICP monitoring (early identification of patients that require more aggressive medical or surgical procedures and the evaluation of response to medical
and/or surgical treatments) outweighs the risk caused by the insertion of the device (intracerebral bleeding and/or infection).

**Considerations on the values and preferences of patients**
For this recommendation in particular, patients and their caregivers did not state any preference that would modify the recommendation.

**Implications on resources**
It is considered that the benefit of applying the recommendation may be cost effective, given that the cost of the complications associated with not using neuromonitoring devices in patients with brain injuries during acute treatment of intracranial hypertension can be much greater than the cost that might arise from their use. It is important to bear in mind that in Colombia there are no economic studies on the implications of this recommendation.

**References**


Flowchart for the process of inclusion in articles

References identified through searches of databases (n=320)
- Pubmed: 199
- Embase: 55
- Biosis: 2
- Scisearch: 12
- Medpilot: 10
- Cochrane: 19
- Tripdatabase: 23

References obtained manually (n=8)

All references obtained (n=328)

Duplicate References (n=23)

References included with title and abstract that were revised (n=305)

Articles not related (n=294)

Revised Articles (n=11)

Excluded articles (n=9)
- The results publication did not allow calculating the R-R: 1

Included articles (n=2)
Algorithm 7
ICP monitoring (question 9)

Adult Patient with severe TBI in ICU

Meets the criteria for ICP monitoring*

ICP monitoring

ICP > 20 mmHg

Start treatment with hyperosmolar therapy (see algorithm question No. 5, hyperosmolar solutions)

*ICP monitoring Criteria
- Glasgow Coma Scale greater than or equal to 3 and less than or equal to 8 after resuscitation
- Abnormal CT (hematoma, contusion, edema, herniation or compression of basal cisterns).
Question 10

In adult patients with severe TBI being treated in an ICU, does selective head cooling, compared to normothermia, decrease neurological disability and mortality at discharge?

Recommendation

- It is suggested that adult patients with severe TBI have selectively and non-invasively cooled their skulls using a recirculating-water system or tapes chilled to 4 degrees centigrade, ensuring that intracerebral temperature can be measured.
  ✓ Weak recommendation in favor of the intervention, moderate quality of evidence.

- It is suggested that patients should be maintained at a body temperature above 36 degrees and below 38 degrees, measured rectally, in order to avoid systemic hypothermia.
  ✓ Weak recommendation in favor of the intervention, moderate quality of evidence.

- It is not recommended to perform the intervention in institutions that do not have a recirculating-water system or tapes chilled to 4 degrees centigrade.
  ✓ Recommendation by strong consensus in favor of the intervention.

Introduction

Head cooling has been proposed as a model of neuroprotection in intensive care for patients with severe TBI. Cooling can be applied invasively and non-invasively, systemically or locally (Lazorthes 1958, Polderman 2004 Miñanbres 2008). The local non-invasive method (selective) may limit the secondary damage associated with systemic induction of hypothermia, which may be related to complications such as cardiac arrhythmia, abnormal coagulation and risk of systemic infections (Sahuquillo 2007). Therefore, selective head cooling is considered a therapeutic alternative in patients with severe TBI in order to decrease the metabolic consumption of cerebral oxygen and reduce refractory intracranial pressure. Various studies have attempted to examine the relationship between systemic hypothermia and functional
outcome in these patients. Studies with systemic hypothermia have not shown a benefit of the procedure. Few studies have evaluated non-invasive selective hypothermia, but this intervention continues to be used with heterogeneity in different health institutions. For this reason it has been decided to include this question for clinical practice guidelines in Colombia.

**Summary of the evidence**

A total of three studies were reviewed to answer the question (Qiu 2006, Liu 2006, Harris 2009). All three studies were randomized clinical trials in which non-invasive selective cooling of the head using external devices were compared with the non-use of the same. The three studies included adult patients with severe TBI and for this reason were included in the analysis. In the first study (Qiu 2006), 90 patients were analyzed and selective cooling was started in 45 of them between 0 and 5.6 hours after admission or emergency surgery, and cooling was maintained for three days. The system maintained a temperature in the skull and neck of around 4 degrees Celsius using an external water recirculation system and ice belts. Acquired average brain temperature was between 33 and 35 degrees centigrade, measured by an intraparenchymal temperature monitor. Rectal temperature was assessed to maintain a systemic temperature of no more than 37 degrees centigrade. Intracranial pressure was lower during the time of the procedure in the intervention group. Good functional outcome (defined as having GOS 4-5) at 6 months was 73.3% in the intervention group, and 51.1% for the group whose heads were not cooled. There were more cases of pneumonia and thrombocytopenia in the intervention group. The platelet count was normalized after treatment ended. There were no abnormalities of heart rate, blood pressure or electrolytes. The second study (Liu 2006) analyzed 66 patients divided into 3 groups; 22 patients were given non-invasive selective cooling, 21 were given mild systemic hypothermia and 23 patients were treated with normothermia. All were adults with severe TBI. The authors evaluated outcome at discharge and at 2 years.
Treatment was continued for 3 days. In the group of selective cooling, success (measured as GOS 4-5) at two years was 72.7%, and in the normothermia group it was 34.8%. There were no differences in infectious complications. The platelet count was found to be decreased in both groups that underwent hypothermia and cooling compared to the control group, but this decrease platelet returned to normal 3 days after completing treatment. Selective cooling was performed with a water recirculation system at 4 degrees centigrade and ice bars at neck level. Brain temperature, measured intraparenchymally, fell to 33 degrees Celsius. There was a significant reduction in intracranial pressure in patients receiving the treatment and also an increase in serum sodium levels. The third study (Harris 2009) used a system called a “cooling cap” in adult patients with severe TBI. 25 patients were analyzed, of which 12 were assigned to treatment and 13 to the control group. The patients in the control group spent more time in the emergency department before being transferred to the ICU. In the group of selective cooling, mortality at hospital discharge was 50%, and in the normothermia group, mortality was 30.8%. Intracranial temperature was reduced to 33 degrees Celsius and the body was heated to maintain a minimum of 36 degrees and avoid systemic hypothermia. Treatment was maintained for 3 days.

Given that the devices used in the three studies are not currently available in Colombia, the working group considered it important to make a consensus to establish a recommendation on selective cooling of adult patients with severe TBI in environments that do not have this equipment. All the participants of the consensus were sent the studies identified in the search, including those who did not meet all the criteria of the PICO question. Subsequently a face-to-face meeting lasting two hours was held. The group was composed of experts working in prehospital care, emergency departments, intensive care and neurosurgery services in different regions of the country, both in public and private institutions (Table 12).
A presentation on the results of the literature review was conducted. For this group, the question raised was: Do you consider that selective head cooling can be performed in adult patients with severe TBI in institutions that do not have the devices reported in the literature? Later, a discussion space was created, in which experts gave their views on the question under discussion. Members of the working group acted as moderators and clarified doubts about the interpretation and analysis of the various studies previously sent. There was one round of voting with 14 experts, in which one of the voters voted for performing the procedure, and the remaining 13 voted against. Therefore, there was further discussion of the risks and benefits, and later, there was strong agreement in favor of not performing the procedure if the institution does not have the appropriate equipment (ice belts, cooling cap and intracerebral temperature measurement).
From evidence to recommendation
In the discussion of the working group, it was decided that the recommendation for selective cooling is weak in favor of the intervention because, although the balance between desired outcomes (improvement in disability and decreased mortality) vs unwanted results (coagulopathy, infection, hydro-electrolyte disturbance) is slightly in favor of cooling, it was recognized that the equipment evaluated in the studies is unavailable for intervention in most institutions in Colombia, and in the same way, the consensus of experts discussed the importance of hospitals having this equipment in order to make an appropriate intervention.

Structural requirements
It is considered that to carry out this recommendation, no infrastructure is required in addition to that, which is already available within the Colombian system of social security in health. Current standards do not provide the necessary elements to establish a procedure of selective head cooling in adult patients with severe TBI. Currently, the procedure is performed without a device designed for this purpose and without measuring the intracerebral temperature, making it difficult to maintain a specific target for the treatment. This inability to control this temperature can generate more complications than benefits.

Considerations on benefits and risks
It is considered that the benefit of implementing selective head cooling (reduction in cerebral metabolic consumption and anti-inflammatory effect) outweighs the risk caused by localized hypothermia (infection and coagulopathy). Keeping in mind that selective hypothermia poses fewer risks than systemic hypothermia, it is vital to control body temperature in order to prevent systemic hypothermia.

Considerations on the values and preferences of patients
For this recommendation in particular, patients and their caregivers did not state any preference that would modify the recommendation.
Implications on resources
It is considered that the benefit of implementing the recommendation may be cost effective, given that the cost of the complications associated with not controlling intracranial hypertension in patients with brain injuries (Cerebral infarction, brain herniation, brain death) can be much greater than the cost that might arise from the use of these local cooling devices. It is important to remember that in Colombia there are no economic studies on the implications of this recommendation.

References
Flowchart for the process of inclusion in articles

References identified through searches of databases (n=352)
- Pubmed: 92
- Embase: 114
- Biosis: 27
- Scisearch: 70
- Medpilot: 18
- Cochrane: 27
- Tripdatabase: 4

References obtained manually (n=2)

All references obtained (n=354)

Duplicate References (n=68)

References included with title and abstract that were revised (n=286)

Articles not related (n=283)

Revised Articles (n=3)

Excluded articles (n=0)

Included articles (n=3)
Algorithm 8  
Hypothermia (question 10)

[Diagram showing decision process]

Adult Patient with severe TBI in ICU and refractory intracranial hypertension

Availability of cooling systems of recirculating water or frozen tapes to 4 degrees Celsius and a device for measuring brain temperature

Yes

Start selective head cooling maintain a body temperature above 36 degrees and below 38 degrees, measured by rectal temperature, in order to avoid the systemic hypothermia

No

Continue handling in ICU (see algorithm question No. 7, Sedation), consider indications for surgery from cerebral edema before 24 h (see algorithm question No. 6)
**Economic Question**

Economic evaluation for rapid sequence intubation in patients with severe traumatic brain injury.

**Objective**

Determine if the Rapid Sequence Intubation (RSI) procedure applied early in prehospital care (PHC) on adult patients diagnosed with severe Traumatic Brain Injury (TBI), is more cost-effective compared with intubation in Hospital Emergency Department (ED).

**Methods**

A decision model was designed to compare the costs and outcomes related to two strategies for performing RSI (PHC or ED) on adult patients with severe TBI. Costs were determined from Colombian practice guidelines. Outcomes were measured using GOS-E adjusted to 3 states of health (neurological outcome level 1 and 2, plus death), at 6 months after the accident; the effectiveness of therapeutic alternatives was taken from existing clinical literature. Based on this information, the incremental cost-effectiveness ratio (ICER) was calculated. Finally, the model was calibrated using indicators of cost-utility (QALY), scenarios of extreme values (univariate) and a Monte Carlo process with 10,000 iterations (multivariate).
Results

The RSI-PHC strategy is more cost effective than the RSI-ED strategy and generates significant savings for the GSSSH. In the base scenario, the ICER is estimated to be -$270 million; models used show that if more RSI procedures were carried out in PHC and fewer in ED, the GSSSH would get better levels of health for their beneficiaries and would use financial resources more efficiently.

Conclusions

Current clinical practice and especially the mechanism of reimbursement for emergency care related to TBI, make the costs of RSI-ED strategy higher than those of RSI-PHC; furthermore, early treatment using RSI for a TBI emergency increases the likelihood of obtaining better neurological outcomes, so the RSI-PHC strategy becomes dominant over RSI-ED.

Revision of economic evaluations present in the literature

The economic question made above is taken as the basis for the systematic review of existing literature, which is a complementary process to the search performed by the clinical team; for this reason the same databases and syntax were used as in the technology assessment process (discussed in the relevant section of the Clinical Practice Guideline of Severe TBI (CPG/TBI)), and the relevant economic terms were also used. Furthermore, the databases recommended by the methodological guideline (MG) were used: Econlit, Embase, MEDLINE/PUBMED, Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) Database. The search process for economic evidence in the literature yielded no results that specifically answered the economic question (and neither did it obtain any results that answered it partially). Therefore, the evaluation used the reference on which the Clinical Team of the working group based their evidence: “Prehospital Rapid Sequence Intubation Improves Functional Outcome for Patients with Severe Traumatic Brain Injury. A Randomized Controlled Trial “published by Bernard et al (2012), in which the authors sought
to determine whether RSI in PHC applied to adult patients (> 16 years) diagnosed with Severe TBI (GCS < 9) improves neurological outcomes measured 6 months post-trauma, compared with intubation procedure made in hospitals.

**Chart 1. Selection of Relevant Studies for the Literature Review.**
Source: Made by the working group based on CDR 2009.
As indicated in the MG, the Economical Evaluation (EE) of the RSI procedure in the CPG/TBI, due to a lack of economic evidence, must be made de novo based on existing data and/or data on clinical effectiveness found by the clinical team of the working group, complemented with data on costs that can be created from the description of the practices related to the treatment of TBI in Colombia and the innovation proposed by the CPG/TBI, such as the procedures described in the guidelines for PHC and emergencies of the Ministry of Health and Social Protection.

**Conclusions**

The final recommendation after the economic assessment is that ambulances of Medicalized Assistance Transport (MAT), which rigorously apply the standard procedures for PHC, must attend to severe TBI events; evidence was found which makes more efficient use of the resources of the GSSSH and helps improve health outcomes.

The economic assessment for the RSI procedure in the CPG/TBI shows that the RSI-PHC strategy, by making use of the resolution capabilities of ambulances or MATs is more cost-effective than the current RSI-ED practice, to the point of being totally dominant over this (negative incremental cost, positive incremental effectiveness); additionally the ICER is located in quadrant VI and its value is optimally well below the WHO threshold of 1 GDP (approx -$270 million compared to $14.5 million.). This result happens basically because standard practice in Colombia loads the system with costs that can be saved; currently, emergencies related to TBI are attended through Basic Assistance Transport (BAT) procedures, but reimbursed at MAT rates, especially because there is a high probability (over 90%) that the cases are traffic accidents and therefore the rate established in the 2013 SOAT (obligatory road insurance) manual applies. In this way the management of an emergency becomes a patient transfer to an ED, at PHC rates. Finally, it is important to clarify that the use of RSI in PHC, although it is regulated in Colombia by technical guides, requires a number of additional factors, some of a logistical nature (such as the effective and efficient functioning of the Regulating Center for Emergencies) other operating (such as the standard number of hours of specific training in intubation required for staff in MAT), which together have implications
in clinical outcomes. As mentioned in the Clinical Practice Guidelines for the Diagnosis and Treatment of Adult Patients with Severe TBI, in its chapter on early intervention by RSI, Colombia must make improvements in PHC so that the procedures applied in this instance reach the level of development seen in the clinical evidence. An example for this case is the Australian PHC system on which Bernard based his study. This whole set of elements would be the ideal base to design a comprehensive and deep Budget Impact Analysis (BIA) from the perspective of the GSSSSH, which would allow the system to have a tool that helps align the requirements of public investment in health with policies in PHC quality and the levels of health of the Colombian population.

The full economic study, including the references used in the production of this study, can be read in Chapter 4 of the full version of this guide.
Abbreviations and Glossary

Abbreviations

AIS: Abbreviated Injury Scale
AMSTAR: A Measurement Tool To Assess Systematic Reviews
ASCOFAME: Asociación Colombiana de Facultades de Medicina (Colombian Association of Medicine Faculties)
BIA: Budget Impact Analysis
BNEE: Brigade Nationale d’Enquêtes Économiques (French National Brigade of Economic Surveys)
BTF: Brain Trauma Foundation
CT: Computerized Tomography
CEA: Cost-Effectiveness Analysis
CENDEX: Centro de Proyectos para el Desarrollo (Center for Development Projects)
COLCIENCIAS: Departamento Administrativo de Ciencia, Tecnología e Innovación (Colombian Administrative Department of Science, Technology and Innovation)
CPA: Cost and Profit Analysis
CSF: Cerebrospinal fluid
CUPS: Clasificación Única de Procedimientos de Salud (Unique Classification of Health Procedures)
DANE: Departamento Administrativo Nacional de Estadística (Colombian National Administrative Department of Statistics)
**DIMDI:** *Deutsches Institut für Medizinische Dokumentation und Information* (German Institute for Medical Documentation and Information)

**EPS:** *Entidad Promotora de Salud* (Colombian Healthcare Provider)

**GCS:** Glasgow Coma Scale

**GDP:** Gross Domestic Product

**GOS:** Glasgow Outcome Scale

**GOS-E:** Glasgow Outcome Scale -Extended

**CPG:** Clinical Practice Guideline

**GRADE:** Grades of Recommendation, Assessment, Development and Evaluation Working Group

**GSSSH:** General Social Security System in Health

**HITS-NS:** Health Information Technology Services of Nova Scotia

**ICER:** Incremental cost-effectiveness ratio

**ICH:** Intracranial Hypertension

**ICP:** Intracranial Pressure

**ICU:** Intensive Care Unit

**ICUR:** The Incremental Cost Utility Ratio

**IETS:** *Instituto de Evaluación Tecnológica en Salud* (Colombian Institute of Technological Evaluation in Health)

**IPS:** *Instituciones Prestadoras de Servicios* (Colombian Healthcare Services)

**LMWH:** Low Molecular Weight Heparin

**MG:** Management Group

**MGEE:** Methodological Guide for Economic Evaluations

**MINSALUD:** *Ministerio de Salud y Protección Social* (Colombian Ministry of Health and Social Protection)

**NPV:** Net Present Value

**NS:** Normal Saline Solution

**PHC:** Pre Hospital Care

**PICO:** Population, Intervention, Comparator and Outcome
**POS:** Plan Obligatorio de Salud (Obligatory Health Plan)

**QALY:** Quality-Adjusted Life Years

**RASS:** Richmond Agitation Sedation Scale

**RSI:** Rapid Sequence Intubation

**SIGN:** Scottish Intercollegiate Guidelines Network

**SISMED:** Sistema Integrado de Suministros de Medicamentos e Insumos Quirúrgicos (Integrated System for the Provision of Medication and Surgical Supplies)

**SISPRO:** Sistema Integral de Información de la Protección Social (Integrated Information System for Social Protection)

**SOAT:** Seguro Obligatorio de Accidentes de Tránsito (Colombian Obligatory Insurance for Traffic Accidents)

**SPSS:** Statistical Product and Service Solutions

**TAB:** Transporte Asistencial Básico (Basic Assistance Transport)

**TAM:** Transporte Asistencial Medicalizado (Medicalized Assistance Transport)

**TBI:** Traumatic Brain Injury

**WHO:** World Health Organization

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**Glossary**

**Advanced life support:** Measures for the advanced management of patients in the emergency department, including invasive methods and use of medication

**Advanced neurological monitoring:** The use of devices to measure the brain’s physiological variables in the intensive care unit

**Amnesia:** Loss of memory

**Bag-valve mask system:** Device that supplies air through the airway to support spontaneous ventilation in patients with respiratory failure
**Basic care transfer unit:** Motor vehicle manned by personnel trained in basic life support, used to transfer patients from the site of an emergency or between hospitals

**Basilar skull fracture:** Disruption of the cranial table in the region of the floor of the skull

**Biosis:** Biological Science Database

**Brain death:** Cessation of brain functional activities after irreversible damage of brain tissue

**Brain drain surgery:** A surgical procedure through which intracranial hematic collections are evacuated

**Brain hernia:** Squeezing of brain tissue through natural spaces in the skull

**Brain inflammation:** Phenomenon of brain tissue which occurs as a cellular response associated with trauma

**Brain necrosis:** Death of brain tissue due to lack of oxygenated blood flow

**Capnography:** A device that allows measurement of carbon dioxide exhaled during respiration

**Cephalea:** Aches and pains located anywhere in the head

**Coagulopathy:** A group of disorders of the coagulation system of the blood, due to which bleeding is prolonged and excessive.

**Cochrane Library Database:** Database of systematic revisions in the Cochrane library

**Controlled clinical trial:** Scientific procedure commonly used in testing medicines or medical procedures randomly

**Computerized tomography (CAT) of the skull:** Brain image made through a computerized system that integrates radiological images of the skull

**Cranial descompression surgery:** A surgical procedure through which a large portion of the skull bone is removed to relieve intracranial pressure
**Craniotomy:** Surgical opening of the cranial cavity

**Cerebral infarction:** Injury caused by lack of blood flow within the brain tissue

**Cerebral ischemia:** Brain state secondary to a reduction in oxygen supply to brain tissue

**Diplopia:** Visual impairment in which objects appear twice

**Disability:** A condition under which certain people have some physical, mental, intellectual or sensory impairment that in the long run affects their way of interacting and participating fully in society

**Depressed fracture:** Depression of a fragment or section of the skull bone, which often compresses the brain and the dura beneath

**Diagnostic heterogeneity:** Variability in diagnoses

**Endotracheal intubation (intratracheal):** Action to introduce a silicone tube through the trachea in order to facilitate the passage of air from outside into the lungs.

**Extradural hematoma:** A buildup of blood located between the skull and the dura mater

**Focal neurological deficit:** Abnormality of the nervous system detected during physical examination

**Forensis:** Journal of the National Institute of Legal Medicine and Forensic Sciences

**Good clinical practice:** International ethical and scientific standards for designing, conducting, recording and reporting studies that involve the participation of human standard.

**Gray Literature:** Any document that is not included in the main search databases

**Hyperkalemia:** Increased blood potassium levels above those accepted as normal

**Hipervolemia:** State of increased body intravascular volume

**Hypertonic solution:** Crystalloid or colloid solution with a high sodium load

**Hypotension:** Blood pressure below the normal limit
**Injury severity index:** Abbreviated injury scale created by the American Medical Association, quantifying the severity of injury to each of the body regions

**Inductor Medication:** Medication associated with a state of hypnosis that is part of rapid sequence intubation

**Intensive care:** Medical specialty dedicated to providing life support or organ systems support in critically-ill patients

**Intracranial hematoma:** A buildup of blood inside the brain tissue

**Intracranial hypertension:** Increased pressure within the structures of the content of the cranial cavity

**Intracranial pressure:** Pressure that exists within the cranial cavity

**Intravenous fluids:** Crystalloid solutions used for resuscitation that create volume within the intravascular space

**Isotonic solution:** Crystalloid or colloid solution with a sodium concentration similar to blood plasma

**Laryngeal Mask:** Alternative airway management device used as part of rescue in case of unsuccessful intubation.

**Laryngoscopy:** Action of visualizing the airway through a laryngoscope

**Level of Evidence:** Hierarchical system, based on tests or research studies, which helps health professionals to assess the strength or solidity of evidence linked to the results of a therapeutic strategy

**Meta-analysis:** A set of statistical tools that is useful to synthesize data from a study group

**Mortality:** The number of deaths in a population

**Neurologic sequelae:** Cognitive, motor or sensory disturbance resulting from a brain injury

**Neuromuscular relaxant:** A drug that induces relaxation of skeletal muscle and that is part of rapid sequence intubation

**Oropharyngeal airway:** A device that keeps the air passage between the mouth and pharynx open

**Otorrhea:** Loss of cerebrospinal fluid through the ear canal
**Outcome**: Final result of an event or occurrence that has been taking place for some time

**Periorbital ecchymosis**: Purplish discoloration of the tissue around the eye socket

**Persistent vomiting**: Emesis on more than two occasions

**Pharmacological anticoagulation**: Inhibition of the process of blood coagulation induced by medications

**Postraumatic seizure**: Abnormal movements generated by pathological cerebral electric shock

**Prehospital care**: Operational and coordination service for urgent medical problems comprising rescue services, health care and transportation provided to sick or injured people outside the hospital

**Pubmed**: Search engine for the Medline database

**Pulse-oximetry**: Monitoring method which evaluates the percentage of oxygen in peripheral arterial blood

**Rapid sequence intubation**: Sequential use of drugs required to carry out the process of intubation

**Refractory intracranial hypertension**: Increased intracranial pressure for more than 5 minutes above 25 mmHg

**Retroauricular ecchymosis**: Purple discoloration in tissue located behind the ear

**Rhinorrhea**: Loss of cerebrospinal fluid through the nasal passage

**Skull fracture**: Disruption of the cranial bone

**Subdural hematoma**: A buildup of blood located between the dura mater and the brain

**Selective hypothermia**: A maneuver of decreasing temperature, applied to one segment of the body (eg head)

**Secondary brain injury**: Physiological disorder in the brain resulting from the body’s natural reaction to a brain injury that is treated inappropriately.

**Systolic blood pressure**: Corresponds to the maximum blood pressure when the heart is contracting
Sedation: Pharmacological induction of a state of decreased consciousness

Search syntax: Combination of all descriptive terms designated for the study which will be used in article search engines

Survival: Time after treatment during which there is no mortality

Systematic review: Review of scientific articles that follow an explicit method to summarize information about a certain topic or health problem

Thromboprophylaxis: Method to prevent the formation of thrombus in peripheral or central veins

Trauma care system: Part of the health model designated for emergency trauma health care

TripDatabase: Medical search engine with an emphasis on medicine based on evidence, questions and clinical guidelines
Annexes
Annex 1

Importance of outcomes

1. Mortality / Survival Neurological disability (GOS, GOSE)
2. Failed Intubation
3. Serum triglyceride concentration
4. Deep venous thrombosis
5. Pulmonary embolism
6. Success rate of intubation in the 1st attempt / systemic complications
7. Hospital/ progression of neurologic damage
8. Important but not critical to take decisions
9. Low importance in decision-making
Annex 2

Inclusion and exclusion tables for full text articles

Question 1a

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<thead>
<tr>
<th>AUTHOR</th>
<th>METHOD</th>
<th>PARTICIPANTS</th>
<th>INTERVENTION</th>
<th>FINAL POINTS</th>
<th>MEETS REQUIREMENTS</th>
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<tr>
<td>Pandor 2012</td>
<td>Meta-analysis and systematic review</td>
<td>Mild TBI; Diagnostic cohorts</td>
<td>Clinical characteristics</td>
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References

Question 1b

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<td>Sue E. Harnan 2011</td>
<td>Systematic review</td>
<td>Mild TBI</td>
<td>Rules for clinical decision making</td>
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<td>Dunning 2004</td>
<td>Meta-analysis</td>
<td>Mild TBI</td>
<td>Factors for the prediction of intracranial hemorrhage</td>
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References
**Question 2**

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<tbody>
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<td>1</td>
<td>DuBose</td>
<td>Observational</td>
<td>2008</td>
<td>Adult patients with severe TBI (head acute injury score &gt; 3)</td>
<td>Admitted to level 1 trauma centers vs level 2 trauma centers</td>
<td>Mortality, complications, progression of neurological damage</td>
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**References**


**Question 3**

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<td>1</td>
<td>Lenartova</td>
<td>Observational</td>
<td>2007</td>
<td>Adults and children with severe TBI</td>
<td>OTI vs No OTI</td>
<td>GOS at 3 months</td>
<td>NO, because the population includes children</td>
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<td>Franshman</td>
<td>Observational</td>
<td>2011</td>
<td>Adults with severe TBI</td>
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<td>GOS at 6 months</td>
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<td>Bernard</td>
<td>RCT</td>
<td>2010</td>
<td>Adults with severe TBI</td>
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<td>GOS-E at 6 months</td>
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<td>Davis</td>
<td>Observational</td>
<td>2005</td>
<td>General population with severe TBI (Adults and children with severe TBI)</td>
<td>OTI Pre-hosp vs OTI Emergency</td>
<td>Mortality</td>
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<td>Gaushe</td>
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<td>2000</td>
<td>Children = 0 &lt; 12 years</td>
<td>OTI vs No OTI</td>
<td>Mortality</td>
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<td>Hartl</td>
<td>Observational</td>
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<td>General population with severe TBI (Adults and children with severe TBI)</td>
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<td>Mortality at 2 weeks</td>
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<td>Bochicci</td>
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<td>2003</td>
<td>14 to 56 year old patients</td>
<td>Prehosp OTI vs emergency OTI</td>
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<td>Adults with moderate and severe TBI</td>
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<td>Mortality</td>
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<td>Bukur</td>
<td>Observational</td>
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<td>Adults with moderate and severe TBI and with AIS = &gt;3</td>
<td>OTI vs No OTI</td>
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<td>Adults with severe TBI; AIS = &gt;3</td>
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<td>Adults with major trauma</td>
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<td>NO, because they evaluated mortality at 6 months</td>
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<td>Davis</td>
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<td>2003</td>
<td>Adults with severe TBI</td>
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<td>Mortality</td>
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<td>Murray</td>
<td>Observational</td>
<td>2000</td>
<td>Patients with severe TBI</td>
<td>OTI vs No OTI</td>
<td>Mortality</td>
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<td>No.</td>
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<td>Eckstein</td>
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<td>2000</td>
<td>Patients with major trauma</td>
<td>OTI vs No OTI</td>
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<td>Winchell</td>
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<td>1997</td>
<td>Patients with severe TBI</td>
<td>None</td>
<td>Mortality</td>
<td>NO, because GOS-E was evaluated at hospital discharge</td>
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References


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<tr>
<td>1</td>
<td>Baker AJ, Rhind SG, Morrison LJ et al.</td>
<td>RCT</td>
<td>2009</td>
<td>Adults with severe skull trauma Glasgow &lt; 8</td>
<td>250 ml of hypertonic saline solution 7.5% and dextran 70</td>
<td>Survival, GOS, GOS-E, FIM, DRS, Biomarkers</td>
<td>No, because it was not compared with normal saline solution</td>
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<td>2</td>
<td>Bulger E, Jurkovich G, Nathens A et al.</td>
<td>RCT</td>
<td>2008</td>
<td>Adults: subgroup of patients with closed skull trauma (Head AIS &gt; 2) and at least 1 prehospital PAS 90 mmHg</td>
<td>250 ml hypertonic NaCl (7.5% NaCl in 6% dextran 70)</td>
<td>Acute respiratory distress syndrome (ARDS) in the 28 days following the injury</td>
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<td>3</td>
<td>Bulger E, May S, Brasel K et al.</td>
<td>RCT</td>
<td>2010</td>
<td>Adult with closed skull trauma, GCS score &lt;8 and PAS &gt; 70 mmHg or 71-90 mmHg; cardiac rhythm &gt;0= 108 bpm</td>
<td>Hypertonic saline solution and Dextran</td>
<td>Survival, GOS-E, DRS</td>
<td>YES</td>
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<td>4</td>
<td>Cooper DJ, Myles PS, McDermott FT et al</td>
<td>RCT</td>
<td>2004</td>
<td>Adult with closed skull trauma and GCS&lt;9 and PAS &lt;100 mmHg (includes polytraumatized patients)</td>
<td>250 ml of hypertonic saline solution 7.5%</td>
<td>Survival, GOS, GOS-E, GCS, FIM</td>
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<td>Morrison LJ, Rizoli S, Schwartz B, Rhind S, Black S, Stuss DT</td>
<td>RCT</td>
<td>2006</td>
<td>Adult with closed skull trauma (GCS &lt;9)</td>
<td>250 ml of hypertonic saline solution</td>
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<td>6</td>
<td>Vassar MJ, Fischer RP, O’Brien PE et al</td>
<td>RCT</td>
<td>1993</td>
<td>Adults: subgroup of patients with severe brain injuries (Head AIS of 4, 5 or 6)</td>
<td>250 ml of Ringers Lactate</td>
<td>Survival</td>
<td>No, because it was not compared with saline solution 7.5%</td>
</tr>
<tr>
<td>7</td>
<td>Vassar MJ, Gannaway WL, Holcroft JW</td>
<td>RCT</td>
<td>1991</td>
<td>Adults: subgroup of patients with severe brain injuries (Head AIS of 4, 5 or 6)</td>
<td>250 ml of hypertonic saline solution 7.5% with dextran 70</td>
<td>Survival</td>
<td>No, because it was not compared with normal saline solution</td>
</tr>
<tr>
<td>8</td>
<td>Vassar MJ, Perry CA, Holcroft JW</td>
<td>RCT</td>
<td>1993</td>
<td>Adults: subgroup of patients with severe brain injuries (Head AIS of 4, 5 or 6)</td>
<td>Normal saline solution 0.9%</td>
<td>Survival</td>
<td>No, because it was not compared with saline solution 7.5%</td>
</tr>
<tr>
<td>9</td>
<td>Lenartova L, Janciak I, Wilbacher I, Rusnak M, Mauritz W.</td>
<td>Observational</td>
<td>2007</td>
<td>Adult with severe skull trauma, GCS &lt;9 after resuscitation or deteriorating GCS &gt; 0 = 8 at 48 hours post-injury and with all relevant information. prehospital data available</td>
<td>Hypertonic saline solution</td>
<td>Mortality, favorable result (defined as a good recuperation or moderate disability) severe disability, vegetative state or death after 6 or 12 months, and the relation of the patient after 90 days</td>
<td>No, because it was not compared with normal saline solution</td>
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<tr>
<td>10</td>
<td>Rhind S, Crnko NT, Baker AJ et al.</td>
<td>RCT</td>
<td>2010</td>
<td>Adult with closed skull trauma, GCS score &lt;9</td>
<td>250 ml of hypertonic saline solution 7.5% with dextran 70</td>
<td>Cell adhesion molecules, TNF-a, IL-10, other biomarkers</td>
<td>No, because it was not compared with normal saline solution</td>
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</tbody>
</table>
References


### Question 5

<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Type of Study</th>
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<th>Intervention</th>
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<th>Meets Requirements</th>
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<tbody>
<tr>
<td>1</td>
<td>Francony</td>
<td>RCT</td>
<td>2008</td>
<td>Adults with severe TBI</td>
<td>Mannitol vs SS 7.45%</td>
<td>GOS, survival</td>
<td>NO, because the outcome is not mortality</td>
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<tr>
<td>2</td>
<td>Ware</td>
<td>Observational</td>
<td>2005</td>
<td>Adults with severe TBI</td>
<td>Mannitol vs SS 23.4%</td>
<td>Reduction in ICP and duration of effect, GOS at discharge</td>
<td>NO, because it did not compare with saline solution 7.5%</td>
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<tr>
<td>3</td>
<td>Vialet</td>
<td>RCT</td>
<td>2003</td>
<td>Adults with severe TBI</td>
<td>Mannitol 20% vs SS 7.5%</td>
<td>Mortality at 3 months</td>
<td>YES</td>
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<td>4</td>
<td>Oddo</td>
<td>Observational</td>
<td>2009</td>
<td>Adults with severe TBI</td>
<td>Mannitol 25% vs SS 7.5%</td>
<td>Changes in PbtO2 and in ICP</td>
<td>NO, because the concentration of mannitol was different to the question.</td>
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<tr>
<td>5</td>
<td>Ichai</td>
<td>Observational</td>
<td>2008</td>
<td>Adults with severe TBI</td>
<td>Mannitol vs sodium lactate</td>
<td>ICP after 4 hours</td>
<td>NO, because the mannitol was not compared with saline solution 7.5%.</td>
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<td>6</td>
<td>Batisson</td>
<td>Observational</td>
<td>2005</td>
<td>Adults with severe TBI</td>
<td>SS 7.5% + dextran 6% vs mannitol 20%</td>
<td>Changes in ICP</td>
<td>NO, because the comparison of solutions does not correspond to the question.</td>
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<td>7</td>
<td>Cottenceau</td>
<td>RCT</td>
<td>2011</td>
<td>Adults with severe TBI</td>
<td>Mannitol vs SS 7.5%</td>
<td>GOS-E but did not give data that allows calculation of RR</td>
<td>NO, because the result does not correspond to the question.</td>
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<td>8</td>
<td>Harutjunyan</td>
<td>RCT</td>
<td>2005</td>
<td>Adults with severe TBI</td>
<td>SS/starch vs mannitol</td>
<td>Mortality</td>
<td>NO, because the solutions compared do not correspond to the question.</td>
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<td>9</td>
<td>Sakellaridis</td>
<td>RCT</td>
<td>2011</td>
<td>Adults and children with severe TBI</td>
<td>Mannitol vs SS 15%</td>
<td>Mortality</td>
<td>NO, because it includes children.</td>
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<td>10</td>
<td>Kerwin</td>
<td>Observational</td>
<td>2009</td>
<td>Adults with severe TBI</td>
<td>Mannitol vs SS 23.4%</td>
<td>Did not report clinical results</td>
<td>NO, because the concentration of saline solution was different to the question.</td>
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<td>11</td>
<td>Mauritz</td>
<td>Observational</td>
<td>2007</td>
<td>Adults with severe TBI</td>
<td>Mannitol vs hypertonic SS, unspecified concentration</td>
<td>Mortality</td>
<td>NO, because the concentration of saline solution was different to the question.</td>
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References


Question 6a

| No. | Author     | Type of Study | Year | Population                                             | Intervention                                         | Result                          | Meets Requirements |
|-----|------------|---------------|------|-------------|-------------------------------------------------------|-----------------------------------------------------|---------------------|--------------------|
| 1   | Seelig     | Observational | 1981 | Patients with TBI, no specifications on severity or age | Early surgery vs late surgery                       | Mortality                       | NO, because the population does not correspond to the question |
| 2   | Wilberger  | Observational | 1990 | Comatose patients (GCS<9) of all ages with acute subdural hematoma | Early surgery vs late surgery                       | GOS at 18 months               | NO, because the population does not correspond to the question |
| 3   | Kotwica    | Observational | 1993 | Adult patients with GCS < 10 who required surgery for SAH | Early surgery vs late surgery                       | GOS at 3 months                | NO, because the population included patients with GCS < 10. |
| 4   | Compagnoni | Observational | 2005 | Adults and children with mild, moderate and severe TBI | Early surgery vs late surgery; decompressive craniectomy vs non-decompressive | Mortality                      | NO, because the population does not correspond to the question |
| 5   | Taussky    | Observational | 2008 | Adults and children with moderate to severe TBI | Early surgery vs late surgery                       | GOS at discharge               | NO, because the population does not correspond to the question |
| 6   | Kim        | Observational | 2009 | Adults and children with mild, moderate and severe TBI | Early surgery vs late surgery                       | Mortality, functional improvement | NO, because the population does not correspond to the question |
| 7   | Karasu     | Observational | 2010 | Adults and children with moderate to severe TBI | Early surgery vs late surgery                       | Mortality                       | NO, because the population does not correspond to the question |
| 8   | Borkar     | Observational | 2011 | Adults over 60 years old with severe TBI | Early surgery vs late surgery                       | Mortality and GOS at 6 months | YES, but it gives global results and not values allow the calculation of the RR |
References


**Question 6b**

<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Type of Study</th>
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<tr>
<td>1</td>
<td>Lee</td>
<td>Observational, retrospective</td>
<td>1998</td>
<td>Patients with epidural hematomas requiring surgery, GCS 3-15</td>
<td>Early surgery vs late surgery</td>
<td>GOS at 1 year</td>
<td>NO, because it included patients with GCS &gt;8.</td>
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<tr>
<td>2</td>
<td>Cohen</td>
<td>Observational, prospective</td>
<td>1996</td>
<td>21 adult patients GCS &lt; 8</td>
<td>Early surgery vs late surgery</td>
<td>Not documented</td>
<td>NO, because the results were not published</td>
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<td>3</td>
<td>Kotwica</td>
<td>Observational, retrospective</td>
<td>1993</td>
<td>Adult patients with GCS &lt; 10 who required surgical treatment for SAH</td>
<td>Early surgery vs late surgery</td>
<td>GOS at 3 months</td>
<td>NO, because it included patients with GCS &gt;8.</td>
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<td>4</td>
<td>Sakas</td>
<td>Observational</td>
<td>1995</td>
<td>Patients with TBI who required craniectomy and were in a state of coma</td>
<td>Early surgery vs late surgery</td>
<td>Mortality, functional recuperation</td>
<td>NO, because it was limited to patients in a coma</td>
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<td>5</td>
<td>Taussky</td>
<td>Observational, retrospective</td>
<td>2008</td>
<td>Adults and children with moderate to severe TBI</td>
<td>Early surgery vs late surgery</td>
<td>GOS at discharge</td>
<td>NO, the population does not correspond to the question</td>
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References


### Question 6c

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<tr>
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<tr>
<td>1</td>
<td>Cianchi</td>
<td>Observational</td>
<td>2012</td>
<td>Adults with severe TBI</td>
<td>Early craniectomy (&lt;24 hours) vs late craniectomy (&gt;24h)</td>
<td>Mortality at discharge and at 6 months, GOS at 6 months</td>
<td>YES</td>
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<tr>
<td>2</td>
<td>Aarabi</td>
<td>Observational</td>
<td>2006</td>
<td>Adults with moderate and severe TBI</td>
<td>Early craniectomy (&lt;48 hours) vs late craniectomy (&gt;48h)</td>
<td>GOS at 3 months</td>
<td>NO, because the population includes patients with moderate TBI.</td>
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<tr>
<td>3</td>
<td>Albanese</td>
<td>Observational</td>
<td>2003</td>
<td>Children and adults with severe TBI</td>
<td>Early craniectomy (&lt;24 hours) vs late craniectomy (&gt;24h)</td>
<td>GOS at 12 months</td>
<td>NO, because the population includes children</td>
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<td>4</td>
<td>Honeybul</td>
<td>Observational</td>
<td>2010</td>
<td>Adults with moderate and severe TBI</td>
<td>Early craniectomy (&lt;30 hours) vs late craniectomy (&gt;30h)</td>
<td>GOS at 18 months</td>
<td>NO, because the population includes patients with moderate TBI.</td>
</tr>
<tr>
<td>5</td>
<td>Wen</td>
<td>Observational</td>
<td>2011</td>
<td>Adults with moderate to severe TBI</td>
<td>Early craniectomy (&lt;24 hours) vs late craniectomy (&gt;24h)</td>
<td>GOS at 6 months</td>
<td>NO, because the population includes patients with moderate TBI.</td>
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References
### Question 7

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<th>INTERVENTION</th>
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<tr>
<td>1</td>
<td>Ghori</td>
<td>RCT</td>
<td>2007</td>
<td>Adults with severe TBI</td>
<td>Propofol 1.5-5 mg/Kg/h vs midazolam 0.1-0.3 mg/kg/h</td>
<td>GOS at 3 months</td>
<td>YES</td>
</tr>
<tr>
<td>2</td>
<td>Sanchez-Izquierdo</td>
<td>RCT</td>
<td>1998</td>
<td>Adults with severe TBI and multisystemic trauma</td>
<td>Propofol 2.12 mg/kg/h vs midazolam 0.19 mg/kg/h</td>
<td>Mortality, hemodynamic changes, adverse effects</td>
<td>NO, because it included patients with other associated traumas.</td>
</tr>
<tr>
<td>3</td>
<td>Sandiumenge</td>
<td>RCT</td>
<td>2000</td>
<td>Adults with severe TBI and multisystemic trauma</td>
<td>Propofol 3.7 mg/kg/h vs midazolam 0.16 mg/kg/h</td>
<td>Quality of sedation, hemodynamic changes, adverse effects</td>
<td>NO, because it included patients with other associated traumas.</td>
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References


### Question 8

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<tr>
<th>No.</th>
<th>Author</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Ali</td>
<td>Case studies and controls</td>
<td>2013</td>
<td>&gt; 15 years with TBI and ICH</td>
<td>Lenox 30 mg sc two times per day (normal creatinine or Heparin 5000 3 times per day TFG &lt; 30 24 hours post-trauma)</td>
<td>Group A without using protocol, group B followed protocol</td>
<td>NO, because it included patients under 16 years old.</td>
</tr>
<tr>
<td>2</td>
<td>Scott</td>
<td>Observational prospective</td>
<td>2002 Cohorts</td>
<td>Adults with TBI and ICH, AIS&gt; 3</td>
<td>Enoxaparin 30 mg sc every 12 hours, 24 hours of initial evaluation im emergency department</td>
<td>No control group</td>
<td>NO, because there was no comparison with unfractionated heparin.</td>
</tr>
<tr>
<td>3</td>
<td>Scott</td>
<td>Observational, prospective study</td>
<td>2008</td>
<td>&gt; 14 years old, blunt TBI</td>
<td>Enoxaparin 30 mg sc every 12 hours, 24 hours initially</td>
<td>No control group</td>
<td>NO, because the population is under 16 years old.</td>
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<td>4</td>
<td>Minshall</td>
<td>Observational</td>
<td>2011</td>
<td>HAIS &gt; 2, &gt; 16 years old, TBI</td>
<td>Compared LMWH 30 mg sc every 12 hours with UFH 5000 u sc three times per day</td>
<td>YES</td>
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<td>5</td>
<td>Salottolo</td>
<td>Observational</td>
<td>2011</td>
<td>TBI, &gt; 18 years old</td>
<td>External compression, LMWH 30 mg sc every 12 hours</td>
<td>Compared time of beginning thrombo prophylaxis</td>
<td>NO, because there was no comparison with unfractionated heparin.</td>
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<td>6</td>
<td>Donald</td>
<td>Observational brain injury, sin TBI</td>
<td>2009</td>
<td>Penetrating brain injury, sin TBI</td>
<td>UFH or LMWH</td>
<td>No prophylaxis, 0-24 hours, 24-48 hours, &gt; 48 hours</td>
<td>NO, because the population does not correspond with the question.</td>
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References


### Question 9

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<td>1</td>
<td>Marmarou</td>
<td>Observational</td>
<td>1991</td>
<td>Adults and children with severe TBI</td>
<td>ICP monitoring</td>
<td>ICP, hypotension</td>
<td>NO, because the population does not correspond.</td>
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<td>2</td>
<td>Lane</td>
<td>Observational</td>
<td>2000</td>
<td>Adults with severe TBI</td>
<td>ICP monitoring vs no monitoring</td>
<td>Survival</td>
<td>YES. But the publication of the results does not allow us to calculate RR</td>
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<tr>
<td>3</td>
<td>Stiefel</td>
<td>Observational</td>
<td>2005</td>
<td>Adults with severe TBI</td>
<td>ICP monitoring vs CP monitoring + monitoring of O2 tissue pressure</td>
<td>Mortality</td>
<td>NO, because there is no comparison with the absence of ICP monitoring.</td>
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<tr>
<td>4</td>
<td>Balestreri</td>
<td>Observational, retrospective</td>
<td>2006</td>
<td>General population with TBI (Adults and children with moderate and severe TBI)</td>
<td>ICP &gt; 20 mm HG vs &lt; 20 mmHG; Cerebral perfusion pressure high vs low</td>
<td>Mortality, GOS-E at 6 months</td>
<td>NO, because the population does not correspond.</td>
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<td>5</td>
<td>Farahvar</td>
<td>Observational</td>
<td>2012</td>
<td>Adults and children with severe TBI</td>
<td>ICP monitoring vs no monitoring</td>
<td>Mortality at 2 weeks</td>
<td>NO, because the population does not correspond.</td>
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<tr>
<td>6</td>
<td>Mauritz</td>
<td>Observational, cohorts, prospective</td>
<td>2008</td>
<td>Adults with moderate and severe TBI</td>
<td>ICP monitoring vs no monitoring</td>
<td>Mortality</td>
<td>NO, because it includes patients with moderate TBI.</td>
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<tr>
<td>7</td>
<td>Barmparas</td>
<td>Observational</td>
<td>2013</td>
<td>Adults with moderate and severe TBI</td>
<td>ICP monitoring vs no monitoring according to trauma center level I or II</td>
<td>Mortality</td>
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<td>8</td>
<td>Chesnutt</td>
<td>RCT</td>
<td>2012</td>
<td>Adults and children with severe TBI</td>
<td>ICP monitoring vs no monitoring</td>
<td>Mortality</td>
<td>NO, because the population does not correspond.</td>
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<td>9</td>
<td>Alali</td>
<td>Observational, cohorts</td>
<td>2013</td>
<td>Adults with severe TBI</td>
<td>ICP monitoring vs no monitoring</td>
<td>Mortality upon discharge</td>
<td>YES</td>
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<td>Shafi</td>
<td>Observational, cohorts</td>
<td>2008</td>
<td>Adults with severe TBI</td>
<td>ICP monitoring vs no monitoring</td>
<td>Mortality upon discharge</td>
<td>YES</td>
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<tr>
<td>11</td>
<td>Thompson</td>
<td>Observational, cohorts</td>
<td>2008</td>
<td>Adults with moderate to severe TBI</td>
<td>ICP monitoring vs no monitoring</td>
<td>Mortality at 12 months</td>
<td>NO, because it includes patients with moderate TBI.</td>
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References


Question 10

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<tr>
<td>1</td>
<td>Harris</td>
<td>RCT</td>
<td>2009</td>
<td>Adults, GCS &lt; 8</td>
<td>Cooling cap vs no cooling cap</td>
<td>Mortality, GOS, FIM</td>
<td>YES</td>
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<tr>
<td>2</td>
<td>Liu</td>
<td>RCT</td>
<td>2006</td>
<td>Adults with severe TBI</td>
<td>Cooling head and neck vs mild systematic hypothermia vs not exposed to hypothermia</td>
<td>GOS</td>
<td>YES</td>
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<tr>
<td>3</td>
<td>Qiu</td>
<td>RCT</td>
<td>2006</td>
<td>Adults with severe TBI</td>
<td>Selective brain cooling vs normothermia</td>
<td>GOS 6 months</td>
<td>YES</td>
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References

## Annex 3

### GRADE Evidence Tables

**Question 2**

**Date:** 2014-01-17  
**Question:** Should level 1 trauma center vs level 2 trauma center be used for adults with traumatic brain injury?  
**Settings:** Trauma center

**Bibliography:** DuBose JJ, Browder T, Inaba K, Teixeira PG, Chan LS, Demetriades D. Effect of Trauma Center Designation on Outcome in Patients With Severe Traumatic Brain Injury. 2008

<table>
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<th><strong>No of patients</strong></th>
<th><strong>Effect</strong></th>
<th><strong>Quality</strong></th>
<th><strong>Importance</strong></th>
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<td>No serious inconsistency</td>
<td>No serious indirectness</td>
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<td>No serious inconsistency</td>
<td>No serious indirectness</td>
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<td><strong>Progression of neurological insult</strong></td>
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<td>No serious inconsistency</td>
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**Question 3**  
**Date:** 2013-09-26  
**Question:** Should Prehospital intubation vs hospital intubation be used for adults with severe trauma brain injury?  
**Settings:**  

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<th>QUALITY</th>
<th>IMPORTANCE</th>
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<tr>
<td><strong>1. Mortality (follow-up 6 months; assessed with: Glasgow Outcome Scale (GOSe) score equal to one (1) at 6 months after injury)</strong></td>
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<tr>
<td>1 Randomised trials</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious¹</td>
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<tr>
<td><strong>2. Bad neurologic outcome (follow-up 6 months; assessed with: Glasgow Outcome Scale (GOSe) score between 2 and 4 at 6 months after injury)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Randomised trials</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious¹</td>
</tr>
<tr>
<td><strong>3. Good neurologic outcome (follow-up 6 months; assessed with: Glasgow Outcome Scale (GOSe) score between 5 and 8 at 6 months after injury)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Randomised trials</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>Serious¹</td>
</tr>
</tbody>
</table>

¹ The 95% confidence interval included no benefit or appreciable benefit.

1 The 95% confidence appreciable benefit or appreciable harm.
**Date:** 2013-11-13  
**Question:** Should non experienced vs experienced prehospital laryngoscopists be used for prehospital intubation?\(^1\)  
**Settings:** Model of difficult intubation  

<table>
<thead>
<tr>
<th>No of Studies</th>
<th>Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Non Experienced</th>
<th>Experienced Prehospital Laryngoscopists</th>
<th>Relative (95% CI)</th>
<th>Absolute Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>First time intubation rates (assessed with: standard laryngoscope)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Randomised trials</td>
<td>Serious(^1) No serious inconsistency</td>
<td>Serious(^3) No serious imprecision</td>
<td>None</td>
<td>0/23 (0%)</td>
<td>14/56 (25%)</td>
<td>RR 0.08 (0 to 1.31)</td>
<td>230 fewer per 1000 (from 250 fewer to 77 more)</td>
<td>@@@O LOW</td>
<td>IMPORTANT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure rate (assessed with: standard laryngoscope)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Randomised trials</td>
<td>Serious(^1) No serious inconsistency</td>
<td>Serious(^3) No serious imprecision</td>
<td>None</td>
<td>16/23 (69.6%)</td>
<td>32/56 (57.1%)</td>
<td>RR 1.21 (0.85 to 1.73)</td>
<td>120 more per 1000 (from 86 fewer to 417 more)</td>
<td>@@@O LOW</td>
<td>CRITICAL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Third-year paramedic students  
\(^2\) Not blinded  
\(^3\) Not TBI patients
**Question 4**
**Date:** 2013-10-21

**Question:** Should hypertonic saline vs SS 0.9% be used for adults with severe TBI?

**Settings:** Prehospital

**Bibliography:** Bulger E, May S, Brasel K et al. Out of hospital hypertonic resuscitation following severe traumatic brain injury 2010

<table>
<thead>
<tr>
<th>QUALITY ASSESSMENT</th>
<th>NO OF PATIENTS</th>
<th>EFFECT</th>
<th>QUALITY</th>
<th>IMPORTANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO OF STUDIES</td>
<td>DESIGN</td>
<td>RISK OF BIAS</td>
<td>INCONSISTENCY</td>
<td>INDIRECTNESS</td>
</tr>
<tr>
<td>Survival at hospital discharge (follow-up 28 days; assessed with: survival (Bulger 2010))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Randomised trials</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
</tr>
</tbody>
</table>

| Bad neurological outcome (follow-up 6 months; assessed with: GOSe < o igual a 4) |
| 1 | Randomised trials | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious | None | 171/341 (50.1%) | 276/582 (47.4%) | RR 1.05 (0.92 to 1.21) | 24 more per 1000 (from 38 fewer to 100 more) | ★★★ MODERATE | CRITICAL |

1 The 95% confidence appreciable benefit or appreciable harm
**Question 5**

**Date:** 2013-10-28

**Question:** Should mannitol vs hypertonic saline be used for adults with severe TBI in the treatment of increased IP?

**Settings:**


<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>No of Patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mannitol</td>
<td>Hypertonic saline</td>
<td>Relative (95% CI)</td>
<td>Absolute</td>
</tr>
<tr>
<td>Mortality (follow-up 3 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Randomised trials</td>
<td>No serious risk of bias ¹</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
</tr>
</tbody>
</table>

¹ Allocation concealment Unclear

² One RR 1.25 with an interval of 0.47 to 3.33, with 20 patients and very few events
**Question 6c**

**Date:** 2013-10-28

**Question:** Should early craniectomy vs late craniectomy be used for adults with severe TBI in patients with refractory intracranial hypertension?

**Settings:** Patients admitted to the ICU of the Emergency Department


<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>No of Patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality (assessed with: ICU mortality)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Observational studies¹</td>
<td>Serious</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
</tr>
<tr>
<td></td>
<td>28.6%</td>
<td>4 more per 1000 (from 136 fewer to 198 more)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Good Neurological outcome (timing of exposure 6 months; assessed with: Glasgow Outcome Scale at 6 months)** | | | | |
| 1 | Observational studies¹ | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | none | 41 cases 21 controls | OR 3.3 (0 to 0) | - | @@@O LOW | CRITICAL |

¹ Case-control  
² Small sample
**Question 7**  
**Date:** 2013-10-10  
**Question:** Should Propofol vs Midazolam be used for sedation in patients with severe traumatic brain injury?  
**Settings:** Intensive care  


<table>
<thead>
<tr>
<th>QUALITY ASSESSMENT</th>
<th>NO OF PATIENTS</th>
<th>EFFECT</th>
<th>QUALITY</th>
<th>IMPORTANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NO OF STUDIES</strong></td>
<td><strong>DESIGN</strong></td>
<td><strong>RISK OF BIAS</strong></td>
<td><strong>INCONSISTENCY</strong></td>
<td><strong>INDIRECTNESS</strong></td>
</tr>
<tr>
<td>1</td>
<td>Randomised trials</td>
<td>None</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>1</td>
<td>Randomised trials</td>
<td>Serious</td>
<td>7/13 (53.8%)</td>
<td>8/15 (53.3%)</td>
</tr>
</tbody>
</table>

1 **No blinding**
**Question 8**

**Date:** 2013-10-22

**Question:** Should low-molecular-weight heparin vs unfractionated heparin be used for adults with severe TBI?

**Settings:** ICU

**Bibliography:** Minshall CT. Safety and Efficacy of Heparin or Enoxaparin Prophylaxis in Blunt Trauma Patients With a Head Abbreviated Injury Severity Score 2 2011.

<table>
<thead>
<tr>
<th>No of Studies</th>
<th>Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Precision</th>
<th>Other Considerations</th>
<th>Low-Molecular-Weight Heparin</th>
<th>Unfractionated Heparin</th>
<th>Relative (95% CI)</th>
<th>Absolute Risk</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Observational studies</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>8/158 (5.1%)</td>
<td>27/171 (15.8%)</td>
<td>RR 0.32 (0.15 to 0.68)</td>
<td>107 fewer per 1000 (from 51 fewer to 134 fewer)</td>
<td>⊗⊗ΟΟ LOW</td>
<td>CRITICAL</td>
<td></td>
</tr>
</tbody>
</table>

**Deep venous trombosis (assessed with:** DVT were diagnosed solely by clinical examination and confirmed with duplex ultrasound)

<table>
<thead>
<tr>
<th>No of Studies</th>
<th>Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Precision</th>
<th>Other Considerations</th>
<th>Low-Molecular-Weight Heparin</th>
<th>Unfractionated Heparin</th>
<th>Relative (95% CI)</th>
<th>Absolute Risk</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Observational studies</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>1/158 (0.63%)</td>
<td>2/171 (1.2%)</td>
<td>RR 0.54 (0.04 to 5.91)</td>
<td>5 fewer per 1000 (from 11 fewer to 57 more)</td>
<td>⊗⊗ΟΟ LOW</td>
<td>CRITICAL</td>
<td></td>
</tr>
</tbody>
</table>

**Pulmonary embolus (assessed with:** A 128 slice helical CT pulmonary angiogram was used to confirm PE in patients when clinically indicated)

<table>
<thead>
<tr>
<th>No of Studies</th>
<th>Design</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Precision</th>
<th>Other Considerations</th>
<th>Low-Molecular-Weight Heparin</th>
<th>Unfractionated Heparin</th>
<th>Relative (95% CI)</th>
<th>Absolute Risk</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Observational studies</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
<td>No serious imprecision</td>
<td>None</td>
<td>0/158 (0%)</td>
<td>7/171 (4.1%)</td>
<td>RR 0.07 (0 to 1.25)</td>
<td>38 fewer per 1000 (from 41 fewer to 10 more)</td>
<td>⊗⊗ΟΟ LOW</td>
<td>CRITICAL</td>
<td></td>
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</table>
Question 9  
Date: 2013-09-30

**Question:** Should Intracranial pressure monitoring vs no intracranial pressure monitoring be used for adults with severe trauma brain injury?  

**Settings:** Intensive care  


<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>No of Patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of Studies</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Risk of Bias</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inconsistency</strong></td>
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<tr>
<td><strong>Indirectness</strong></td>
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</tr>
<tr>
<td><strong>Imprecision</strong></td>
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<td></td>
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<tr>
<td><strong>Other Considerations</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Intracranial Pressure Monitoring</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>No Intracranial Pressure Monitoring</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Relative (95% CI)</strong></td>
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<tr>
<td><strong>Absolute</strong></td>
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<tr>
<td><strong>Quality</strong></td>
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<tr>
<td><strong>Importance</strong></td>
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<table>
<thead>
<tr>
<th>2. Hospital Mortality (Shafi 2008) (follow-up to discharge)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1   Observational studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. Mortality (Alali 2007) (follow-up to discharge)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1   Observational studies</td>
</tr>
</tbody>
</table>

¹ Selection bias, for blindness and execution.
**Question 10**  
**Date:** 2013-12-04  
**Question:** Should selective brain cooling vs normothermia be used for severe TBI?  
**Settings:** ICU  
**Bibliography:** Harris 2009; Qiu 2006; Liu 2006

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>No of Patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality (assessed with: hospital mortality)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Randomised trials</td>
<td>No serious risk of bias</td>
<td>No serious inconsistency</td>
<td>No serious indirectness</td>
</tr>
</tbody>
</table>

| **Good neurological outcome (follow-up 6 months; assessed with: GOS score of 4 to 5)** | | | | |
| 1 | Randomised trials | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious² | None | 33/45 (73.3%) | 23/45 (51.1%) | RR 1.43 (1.02 to 2.00) | 220 more per 1000 (from 10 to more to 511 more) | ☒ ☒ ☒ | MODERATE | CRITICAL |

| **Good neurological outcome (follow-up 2 years; assessed with: GOS score of 4 to 5)** | | | | |
| 1 | Randomised trials | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision² | None | 16/22 (72.7%) | 8/23 (34.8%) | RR 2.09 (1.13 to 3.86) | 379 more per 1000 (from 45 more to 995 more) | ☒ ☒ ☒ ☒ | HIGH | CRITICAL |

¹ The 95% confidence interval included no benefit or appreciable benefit, this study was too small to be powered to detect a difference in mortality  
² The 95% confidence interval included no benefit or appreciable benefit.
## Richmond agitation/sedation scale (RASS)

<table>
<thead>
<tr>
<th>POINTS</th>
<th>CATEGORIES</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative</td>
<td>Violent or combative, a risk for staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
<td>Tries to remove tubes or catheters or is aggressive with staff</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Uncoordinated movements or fights the respirator</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
<td>Anxious but without aggressive or vigorous movements</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td>Tends to be asleep, but is able to be awake for more than 10 seconds (opens eyes to voice)</td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>Awake (opens eyes) for less than 10 seconds in response to voice</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
<td>Movements without opening eyes in response to voice</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
<td>No response to voice, but moves or opens eyes to physical stimulation</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
<td>No response to voice or physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable</td>
<td>Sin respuesta a la voz o estímulo físico</td>
</tr>
</tbody>
</table>

### Procedure

1. Observe the patient. Is (s)he alert and calm? (Score 0). Is (s)he restless or agitated (score +1 to +4)?
2. If the patient is not alert, call him/her by his/her name and see if (s)he opens his/her eyes and makes eye contact.
3. Repeat if necessary.
4. The patient wakes up and opens eyes, maintaining visual contact for more than 10 seconds: score -1.
5. The patient wakes up and opens eyes, maintaining visual contact for less than 10 seconds: score -2.
6. The patient moves in response to voice but does not open eyes: score -3.
7. If the patient doesn’t respond to voice, physically stimulate him/her by moving the shoulder or pressing the sternum.
8. If the patient moves after physical stimulation: score -4.
9. If the patient doesn’t move after any physical stimulation: score -5.

Clinical Practice Guideline
Diagnosis and treatment of adult patients with severe Traumatic Brain Injury
Guide for Health Professionals

gpc.minsalud.gov.co