Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. N Engl J Med 2012;367:2471-81. DOI: 10.1056/NEJMoa1207363

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We would like to thank our DSMB committee members for their guidance throughout this project: M.R. Bullock, (Chair), R. Diaz-Arrastia, M.A. Foulkes, J.I. Suarez, L. Artiola; as well as NIH staff associates R. Hicks and J. Odenkirchen.

RCT Recruitment Hospitals

Original Hospitals

Hospital Viedma – Cochabamba, Bolivia

6 bed ICU: 320 bed general ward

167 cases screened in 38 months (53/year), 76 cases randomized

Hospital San Juan de Dios – Santa Cruz de la Sierra, Bolivia

7 bed ICU; 270 bed general ward

173 cases screened in 38 months (55/year), 88 cases randomized

Hospital Japones – Santa Cruz de la Sierra, Bolivia

6 bed ICU; 180 bed general ward

156 cases screened in 38 months (49/year), 69 cases randomized

Additional Hospitals

Hospital San Juan de Dios -Tarija, Bolivia

6 bed ICU; 250 bed general ward

79 cases screened in 23 months (41/year), 52 cases randomized

Hospital de Especialidades Eugenio Espejo - Quito, Ecuador

12 bed ICU; 446 bed general ward

24 cases screened in 7 months (41/year), 20 cases randomized

Hospital Luis Vernaza, - Guayaquil, Ecuador

37 bed ICU; 836 bed general ward

49 cases screened in 13 months (45/year), 19 cases randomized

Inclusion/exclusion criteria

Inclusion Criteria

- Traumatic brain injury
- GCS $\leq$ 8 on admission or within first 48 hours after injury
- admission to study hospital within 24 hours of injury
- No foreign object in the brain parenchyma.
- Age > 12
- Randomized:
    - within 24 hours of injury [for patients with GCS $\leq$ 8 on admission] or
    - within 24 hours of deterioration [patients deteriorating to GCS $\leq$ 8 within 48 hours of injury]

Exclusion Criteria

- GCS of 3 with bilateral fixed and dilated pupils
- No consent
- Pregnant
- Prisoner
- No beds available in ICU
- No ICP monitor available
- Non-survivable injury
- Other (e.g., Pre-injury life expectancy under 1 year)
- Pre-existing neurological disability that would confound outcome

Treatment Protocols - General

Treatment protocol: We strongly suggest using these interventions whenever available and/or possible.

1. Patient monitoring measures
    a. Place patient on mechanical ventilation (VM)
    b. Place continuous SaPO2 and EtCO2 monitors
    c. Insert indwelling urinary catheter to monitor urine output
    d. Insert arterial catheter for arterial mean pressure monitoring
    e. Insert central venous catheter for infusion of solutions and central venous pressure monitoring.
    f. Monitor neurological clinical status each hour
        i. Pupils
        ii. GCS
        iii. etc
    g. Brain CT
        i. To evaluate evolution 48 hours after the admission CT
        ii. To evaluate evolution 5-7 days after the admission CT
        iii. p.r.n.
2. General measures
    a. Head positioning 30º
    b. Head and neck in neutral position and aligned
    c. Avoid hyperthermia
        i. Defined as central temperature $\geq$ 38 º C
            1. Non-drug measures (cooling)
            2. Dipirona (Metamizole sodium)
    d. Early enteral nutritional support
        i. Before 48 hours
        ii. 25 Kcal/kg weight

e. Pharmacologic prophylactic of post traumatic seizures
    i. Phenytoin (IV or PO)
        1. Load and maintenance dose as is being giving in each hospital
f. Gastric bleeding prophylaxis
    i. Ranitidine or Omeprazol
g. Avoid decubitus lesions
h. Deep venous thrombosis prophylaxis
i. Frequent tracheal suctioning with sterile technique to prevent pulmonary infections

3. Routine CT scans
    a. First CT: on Hospital admission
    b. Second CT: 48 hours after the first CT
    c. Third CT: 5-7 days after the first CT

Treatment Protocols – ICP Group

Guidelines for the Management of Severe Traumatic Brain Injury Patients:

ICP Monitor Group

1. Required patient monitoring measures
    a. Place ICP monitor
        i. **If the initial placement of the ICP monitor is delayed due to contraindications (eg coagulopathy), then the contraindication must be corrected as rapidly as possible and catheter implantation be performed as soon as the contraindication is removed.**
        ii. **In the case of an ICP monitor failure due to catheter breakage, unintentional removal of catheter, or any other damage or compromise of catheter every attempt should be made to replace the catheter with a new properly functioning one.**
        iii. **Every attempt should be made to insert a new ICP monitor following a cranial operative procedure.**
2. Additional patient monitoring measures: We strongly suggest using these interventions whenever available and/or possible.
    a. Place continuous SaO2 and EtCO2 monitors
    b. Insert indwelling urinary catheter to monitor urine output
    c. Insert arterial catheter for arterial pressure monitoring
    d. Insert central venous catheter for infusion of solution and central venous pressure monitoring
    e. Monitor clinical neurological status each hour
        i. Pupil size and reactivity
        ii. GCS
    f. Obtain brain CT
        i. To evaluate evolution 48 hours after the admission CT
        ii. To evaluate evolution 5-7 days after the admission CT
        iii. As needed based on patient clinical condition
3. General management measures
    a. Place patient on mechanical ventilation, goal SaO2 > 90% and PaO2 > 60 mmHg

b. Use adequate sedation and analgesia

    i. Acceptable medications include benzodiazepines, opioids, propofol and low dose barbiturates

        1. Low dose barbiturate dosing:

            a. Thiopental (Pentothal) 1-2 mg/kg/hr IV continuous infusion (approx. 1.5-3 gm/day)

c. Maintain head of bed at 30º

d. Maintain head and neck aligned and in neutral position

e. Actively monitor body temperature and treat hyperthermia

    i. Hyperthermia defined as central temperature ≥ 38ºC

    ii. Non-pharmaceutical cooling measures

        1. Cooling blanket, ice packs

    iii. Pharmaceutical cooling measures

        1. Dipirona (Metamizole sodium)

f. Early enteral nutritional support

    i. Initiate within 48 hours of injury

    ii. Give 25 Kcal/kg patient weight per day

g. Pharmacologic prophylaxis for early post traumatic seizures

    i. Phenytoin (IV or PO)

        1. Loading and maintenance doses as per individual hospital guidelines

        2. Continue for 7-28 days

h. Gastric bleeding prophylaxis

    i. Ranitidine or Omeprazole (IV or PO)

        1. Administer as per individual hospital guidelines

i. Prevent decubitus lesions and treat as indicated

j. Deep venous thrombosis prophylaxis

k. Frequent tracheal suctioning with sterile technique to prevent pulmonary infections

l. Maintain Hb ≥ 7 mg/dL, use blood transfusions as needed

4. CT scans

a. First CT: upon hospital admission

b. Second CT: 48 hours after the first CT

c. Third CT: 5-7 days after the first CT

d. Additional CT scans as needed based on patient clinical condition

5. Treatment Goals for adequate cerebral perfusion and oxygenation

    a. ICP ≤ 20 mmHg

    b. Cerebral Perfusion Pressure (CPP) 50-70 mmHg

    c. Arterial blood oxygen saturation (SaO2) > 90% or PaO2 > 60 mm Hg

6. Initial Therapeutic Interventions

    a. Normal saline solution (0.9% NaCl) to obtain a CVP of 10-12 cmH2O

    b. Vasopressors when necessary to obtain a systolic blood pressure (SBP) > 90 mmHg or mean arterial pressure (MAP) > 70 mmHg **prior to ICP monitoring (use CPP after monitoring begins).**

    c. Maintain PaCO2 35-40 mmHg if CT is normal

        i. In Cochabamba, correct for altitude and maintain PaCO2 32-36 mmHg.

    d. If a space-occupying lesion exists, surgical evacuation is indicated if possible

7. Specific therapeutic interventions-**ICP Monitor with Elevated ICP Treatment algorithm. Use the following treatment interventions sequentially when ICP is elevated or not responding to basic treatment. Note that clinically significant ICP elevation (not resolving within 5 minutes) requires treatment, which should be reflected by an increase in the Therapeutic Intensity Level (TIL) for that hour. Failure of ICP response after 20 minutes should prompt further treatment.**

    a. Maintain CPP between 50-70 mmHg

        i. Every effort should be made to insert an arterial line for continuous MAP monitoring

        ii. If arterial line cannot be placed then calculate MAP from non-invasive blood pressure monitoring every hour to calculate CPP

    b. Ventricular drainage should be considered if available. If an intraparenchymal catheter is already inserted, consider **placing the ventricular drain separately.** Drainage of intraventricular fluid should be intermittent, with removal of the smallest volume of fluid necessary to control intracranial pressure and used for the shortest period of time possible. **It is suggested that drainage be for two minutes and the ventricular catheter then be clamped and the PIC rechecked. When both an intraparenchymal monitor and a ventricular catheter are present, the intraparenchymal device should**

be used to measure the pressure. Note that the ventricular catheter should be clamped when measuring the pressure using either monitor to ensure accuracy.

c. Neuromuscular blockade should be used, suspend if ICP not responding

d. Mild hyperventilation to maintain PaCO2 30-35 mmHg (PaCO2 28-32 mmHg in Cochabamba)

e. Hyperosmolar/hypertonic therapy

    i. Mannitol should be used first except in the following situations (HHH):

        a. Arterial Hypotension

        b. Hypovolemia

        c. Hyponatremia

    2. Hyperosmolar (Mannitol) therapy guidelines and dosing

        a. Plasma osmolarity **or tonicity** should be monitored at least every 12-**24** hours

            i. Plasma osmolarity **or tonicity** should be calculated using the following formulae:

                1. Osmolarity = 2 * (Na) + (BUN/ 2.8) + (Glucose/18)

                    a. Tonicity = 2 * (Na + K) + (Glucose/18)

            ii. Hyperosmolar therapy should be suspended for plasma osmolarity > 320 **or tonicity > 340**

        b. Mannitol dosing regimen using 20% Mannitol bolus:

            i. For ICP elevation > 20 mmHg give 0.25-1 gm/kg 20% Mannitol bolus

            ii. Extra doses can be administered for sustained elevation of ICP if plasma osmolarity < 320

    3. Hypertonic saline therapy guidelines and dosing

        a. Hypertonic saline should only be used in cases of HHH as described above

        b. Plasma osmolarity **or tonicity** and serum sodium should be monitored every 12-**24** hours

            i. Plasma osmolarity **or tonicity** should be calculated using the following formulae:

1. Osmolarity = 2 * (Na) + (BUN/ 2.8) + (Glucose/18)

2. **Tonicity = 2 * (Na + K) + (Glucose/18**

ii. **Hypertonic saline therapy should be suspended for plasma osmolarity > 360 or tonicity > 380 or serum sodium > 160**

c. Hypertonic saline dosing regimen using 5%NaCl solution bolus:

i. 80ml normal saline (0.9%NaCl) + 20ml 20%NaCl = 100ml 5%NaCl solution

ii. 100ml IV given over 1 hour, may repeat as needed for sustained elevations in ICP if plasma osmolarity < **360** and serum sodium < **160**

f. When increasing the therapeutic intensity level obtain a CT scan if possible

8. Neuroworsening requires increased therapeutic intensity level, including decompressive craniectomy when necessary and available. Any one or all of the following therapeutic interventions should be utilized based on patient conditions.

a. Neuroworsening defined as:

1. Decrease in the motor GCS $\geq$ 2

2. New loss of pupil reactivity

3. Interval development of pupil asymmetry of $\geq$ 2mm

4. New focal motor deficit

5. Herniation syndrome

ii. Mannitol dosing regimen using 20% Mannitol bolus:

1. For ICP elevation > 20 mmHg give 0.25-1 gm/kg 20% Mannitol bolus

2. Extra doses can be administered for sustained elevation of ICP if plasma osmolarity < 320

iii. Increase hyperventilation (HV)

1. Maintain PaCO2 of 25-30 mmHg (PaCO2 22-28 mmHg in Cochabamba)

2. Use for shortest time period possible to reverse neurological deterioration

b. If no response, stop HV and use barbiturates

i. High dose IV barbiturates

1. **Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion for 3 days**

2. **Hypotension must be avoided**

c. Head CT is strongly suggested if possible

9. Second tier therapy to be considered in salvageable patients **under conditions such as:**

a. To be considered in case of:

i. ICP not responding to first tier therapy

ii. **Persistent neuroworsening not responding to an increased therapeutic intensity level (as indicated above). CT is recommended, if possible.**

iii. **Follow-up CT (eg day 5 CT) showing Inadequate response to treatment such as persistent edema**

b. Primary options

i. Decompressive craniectomy

ii. High dose IV barbiturates:

1. **Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion (approx. 4-6 gm/day)**

2. **Hypotension must be avoided**

c. Other options

i. Hyperventilation to maintain PaCO2 25-30 mmHg (PaCO2 22-28 mmHg in Cochabamba), use for shortest time period possible to reverse neurological deterioration

ii. Hypothermia

iii. **Lund therapy**

10. Management following decompressive craniectomy

a. Every attempt should be made to insert a new ICP monitor post-operatively, using techniques such as:

1. **Ventriculostomy**

2. **Placing another bolt through an Harborview peninsula left along the margins of the craniectomy**

ii. If placement of the new ICP monitor is problematic, contact Gustavo Petroni, MD (mobile telephone +549-341-514-7543, home telephone +54-341-482-7588, fax +54-341-423-1087, e-mail gustavopetroni@gmail.com) **or Silvia**

Lujan, MD, (mobile telephone +549-341-560-9239, home telephone +54-341-440-2056, fax +54-341-423-1087, e-mail silviablujan@gmail.com) **immediately.**

b. Use adequate sedation and analgesia

c. Mild hyperventilation to maintain PaCO2 30-35 mmHg (PaCO2 28-32 mmHg in Cochabamba)

d. If ICP monitor is placed, treat ICP elevations > 20 as indicated above.

11. Intracranial pressure definitions

    a. Treatable intracranial hypertension:

        i. ICP > 20 mmHg for > 5 minutes

    b. Treatment failure:

        i. ICP not reduced to ≤ 20 mmHg within 20 minutes after a treatment intervention is initiated, and

        ii. Persistent elevation in ICP > 20 mmHg requires increase in therapeutic intensity level

12. Investigation of the patient with intracranial hypertension: After assessment of the following factors and initiation of appropriate interventions as indicated below, if the interventions are ineffective in reducing ICP, increase the therapeutic intensity level.

    a. Check for factors that could increase ICP

    b. Pain or agitation: consider increasing sedation/analgesia

    c. Respiratory agitation, consider the following:

        i. Stopping the procedure

        ii. Lidocaine IV or ET (endotracheal tube)

        iii. Technique modification

    d. Patient manipulation and rotation, consider the following:

        i. Stopping the procedure

        ii. Increasing sedation/analgesia

        iii. Technique modification

    e. Endotracheal tube (ET) problems, consider the following:

        i. Change the ET holder

        ii. Change the ET tube care techniques

    f. Elevated intrathoracic pressure or elevated PEEP, consider the following:

i. Drain any hemopneumothorax

ii. Change ventilator technique

g. Raised intra-abdominal pressure: consider decompressive laparotomy

h. Evidence of seizures: consider evaluation and treatment

i. Check laboratory and vital signs values

i. Hyperthermia: consider reducing the temperature to < 38ºC

ii. Increased PaCO2: consider increasing ventilatory rate

iii. Hypoxia: consider increasing fraction of inspired oxygen

iv. Abnormal CPP:

1. Consider increasing MAP with fluids or vasopressors

2. Consider reducing ICP with sedation and analgesia, hyperventilation, hyperosmolar/hypertonic therapy, and/or high dose barbiturates

v. Hyponatremia: consider correcting plasma electrolytes

j. If you feel that the intracranial situation may have changed, obtain head CT when possible

13. ICP monitor removal:

a. Consider removal of catheter if ICP ≤ 20 mmHg for ≥ 24 hours WITHOUT treatment

b. Confounding factors that may require longer monitoring:

i. Hemodynamic instability

ii. Need for intraoperative monitoring during extracranial surgery

iii. "Clinical judgment"

14. Contraindicated treatments

a. Corticosteroids for brain injury treatment

b. Prophylactic hyperventilation

c. Use of anticonvulsants for prophylaxis of late epilepsy (beyond 28 days)

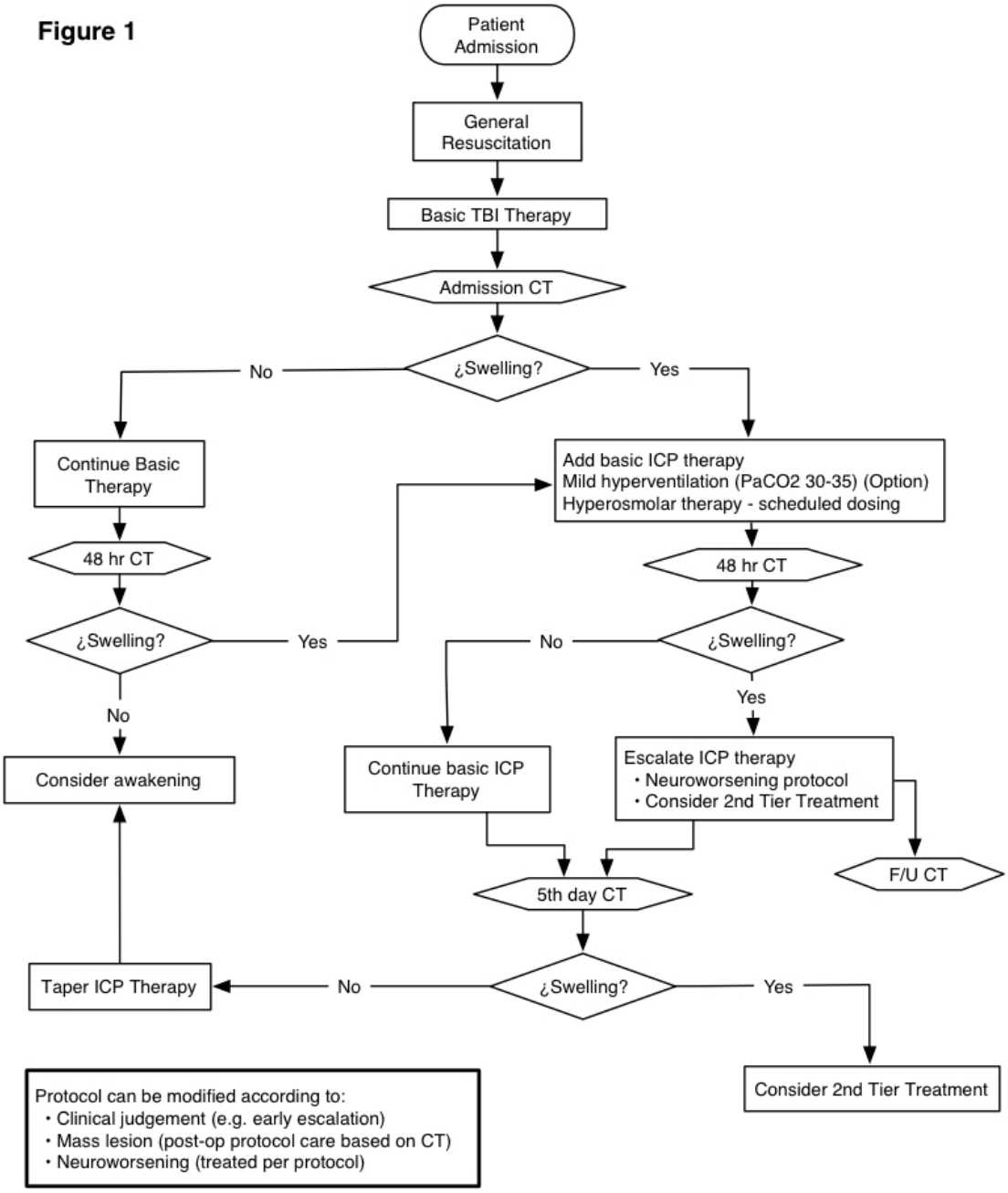
Treatment Protocols – ICE Group

Guidelines for the Management of Severe Traumatic Brain Injury Patients:

Imaging and Clinical Exam (ICE) Group

The guidelines are presented below and are also summarized in Figures 1 and 2.

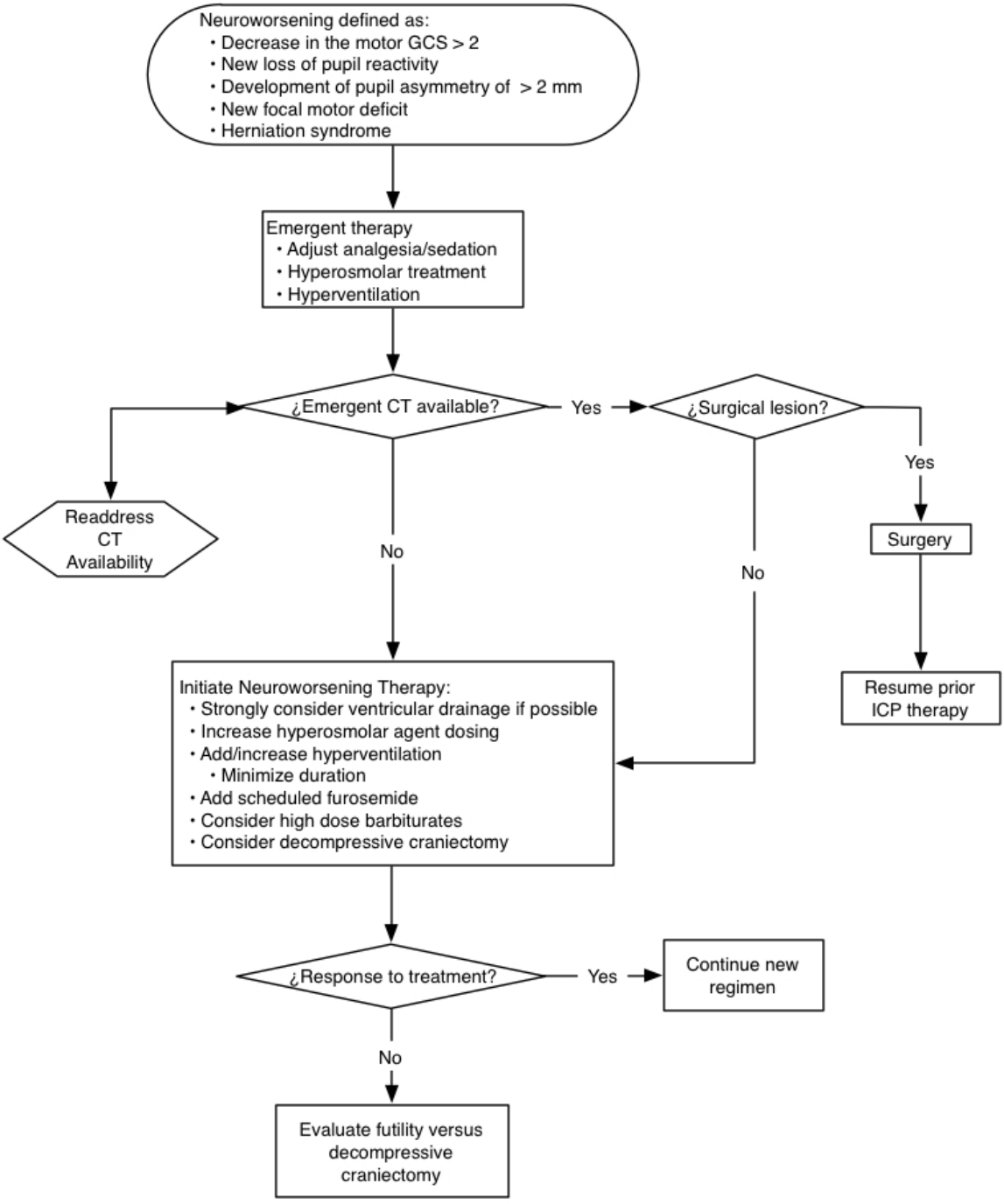
Figure 1



This protocol could be modified:

- By clinical judgment (i.e. DC or barbiturates could be used earlier on)
- Mass lesion on CT scans (procedure to evacuate if it is indicated and then continuing with the protocol based on CT findings)
- Neuroworsening (NW) whenever occurs should be treated as follows (see next)

Figure 2



1. Patient monitoring measures: We strongly suggest using these interventions whenever available and/or possible.

    a. Place continuous SaO2 and EtCO2 monitors

b. Insert indwelling urinary catheter to monitor urine output

c. Insert arterial catheter for arterial pressure monitoring

d. Insert central venous catheter for infusion of solution and central venous pressure monitoring

e. Monitor clinical neurological status each hour

    i. Pupil size and reactivity

    ii. GCS

f. Obtain **brain** CT

    i. To evaluate evolution 48 hours after the admission CT

    ii. To evaluate evolution 5-7 days after the admission CT

    iii. As needed based on patient clinical condition

2. General management measures

    a. Place patient on mechanical ventilation, goal SaO2 > 90% and PaO2 > 60 mmHg

    b. Use adequate sedation and analgesia

        i. Acceptable medications include benzodiazepines, opioids, propofol and low dose barbiturates

            1. Low dose barbiturate dosing:

                a. Thiopental (Pentothal) 1-2 mg/kg/hr IV continuous infusion (approx 1.5-3 gm/day)

    c. Maintain head of bed at 30º

    d. Maintain head and neck aligned and in neutral position

    e. Actively monitor body temperature and treat hyperthermia

    f. Hyperthermia defined as central temperature $\geq$ 38ºC

        i. Non-pharmaceutical cooling measures

            1. Cooling blanket, ice packs

        ii. Pharmaceutical cooling measures

            1. Dipirona (Metamizole sodium)

    g. Early enteral nutritional support

        i. Initiate within 48 hours of injury

        ii. Give 25 Kcal/kg patient weight per day

h. Pharmacologic prophylaxis for early post traumatic seizures

i. Phenytoin (IV or PO)

1. Loading and maintenance doses as per individual hospital guidelines

2. Continue for 7-28 days

i. Gastric bleeding prophylaxis

i. Ranitidine or Omeprazole (IV or PO)

1. Administer as per individual hospital guidelines

j. Prevent decubitus lesions and treat as indicated

k. Deep venous thrombosis prophylaxis

l. Frequent tracheal suctioning with sterile technique to prevent pulmonary infections

m. Maintain Hb ≥ 7 mg/dL, use blood transfusions as needed

3. CT scans

a. First CT: upon hospital admission

b. Second CT: 48 hours after the first CT

c. Third CT: 5-7 days after the first CT

d. Additional CT scans as needed based on patient clinical condition

4. Treatment Goals for adequate cerebral perfusion and oxygenation

a. Avoid hypotension - systolic blood pressure (SBP) > 90 mmHg, mean arterial pressure (MAP) > 70 mmHg

b. Arterial blood oxygen saturation (SaO2) > 90% or PaO2 > 60 mm Hg

5. Initial therapeutic interventions

a. Normal saline solution (0.9% NaCl) to obtain a CVP of 10-12 cmH2O

b. Vasopressors when necessary to obtain a SBP > 90 mmHg **or mean arterial pressure (MAP) > 70 mmHg**

c. Maintain PaCO2 35-40 mmHg if CT is normal

i. In Cochabamba, correct for altitude and maintain PaCO2 32-36 mmHg

d. If a space-occupying lesion exists, surgical evacuation is indicated if possible

6. Specific therapeutic interventions-**Standard (Non-Monitored) Therapy**

a. After optimized sedation and analgesia, hyperventilation and hyperosmotic therapy should be started simultaneously if there is evidence of edema on CT, as indicated as following:

1. Compressed peri-mesencephalic cisterns

2. Midline shift

3. Cortical sulcal compression / effacement

b. Mild hyperventilation

i. Maintain PaCO2 30-35 mmHg (PaCO2 28-32 mmHg in Cochabamba)

c. Hyperosmolar/Hypertonic Therapy

i. Mannitol should be used first except in the following situations (HHH):

a. Arterial Hypotension

b. Hypovolemia

c. Hyponatremia

2. Hyperosmolar (Mannitol) therapy guidelines and dosing

a. Plasma osmolarity **or tonicity** should be monitored at least every 12-**24** hours

i. Plasma osmolarity **or tonicity** should be calculated using the following formulae:

1. Osmolarity = 2 * (Na) + (BUN/ 2.8) + (Glucose/18)

2. **Tonicity = 2 * (Na + K) + (Glucose/18)**

ii. Hyperosmolar (Mannitol) therapy should be suspended for plasma osmolarity > 320 **or tonicity > 340**

b. Mannitol dosing regimen using 20% Mannitol bolus:

i. 100ml (20gm) IV every 3-4 hours for the first 3 days, then

ii. 80ml (16gm) IV every 3-4 hours on day 4, then

iii. 60ml (12gm) IV every 3-4 hours on day 5, then

iv. 40ml (8gm) IV every 3-4 hours on day 6 and suspend

3. Hypertonic saline therapy guidelines and dosing

a. Hypertonic saline should only be used in cases of HHH as described above

b. Plasma osmolarity **or tonicity** and serum sodium should be monitored at least every 12-**24** hours

i. Plasma osmolarity **or tonicity** should be calculated using the following formulae:

1. Osmolarity = 2 * (Na) + (BUN/ 2.8) + (Glucose/18)

2. **Tonicity = 2 * (Na + K) + (Glucose/18)**

ii. Hypertonic saline therapy should be suspended for plasma **osmolarity > 360 or tonicity > 380 or serum sodium > 160**

c. Hypertonic saline dosing regimen using 5%NaCl solution bolus:

i. 80ml normal saline (0.9%NaCl) + 20ml 20%NaCl = 100ml 5%NaCl solution

ii. 100ml IV every 4-12 hours for 6 days then suspend

d. High dose IV barbiturates

i. Use after hyperventilation and hyperosmolar/hypertonic therapies

ii. Should be used if second CT shows evidence of compressed PMC

iii. Dosing: **Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion for 3 days (approx 4-6 gm/day)**

iv. Hypotension must be avoided

7. Neuroworsening requires increased therapeutic intensity level, including decompressive craniectomy when necessary and available. Any one or all of the following therapeutic interventions should be utilized based on patient conditions.

a. Neuroworsening defined as:

1. Decrease in the motor GCS $\geq$ 2

2. New loss of pupil reactivity

3. Interval development of pupil asymmetry of $\geq$ 2mm

4. New focal motor deficit

5. Herniation syndrome

ii. **Hypertonic therapy**:

1. **Additional** mannitol dosing regimen using 20% Mannitol bolus:

i. 200ml (40gm) IV every 3-4 hours for 1 day, then

ii. 100ml (20gm) IV every 3-4 hours for 2 days, then

iii. 80ml (16gm) IV every 3-4 hours on day 4, then

iv. 60ml (12gm) IV every 3-4 hours on day 5, then

v. 40ml (8gm) IV every 3-4 hours on day 6 and suspend

b. High dose mannitol at 0.5 – 1 gm/kg per dose should be used in the case of acute neurological deterioration and as a temporizing measure prior to decompressive craniectomy if there is no response to medical management. The above duration of treatment (6 days) should be followed only when neurosurgical intervention is not available.

c. Contraindicated in patients with HHH

i. **Use hypertonic saline**

d. **Hypertonic saline – doses as above**

iii. Increase hyperventilation (HV)

1. Maintain PaCO2 of 25-30 mmHg (PaCO2 22-28 mmHg in Cochabamba)

2. Use for shortest time period possible to reverse neurological deterioration

3. If no response, stop HV and use barbiturates

iv. High dose IV barbiturates

1. Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion for 3 days

2. Hypotension must be avoided

v. Furosemide 20mg IV every 8 hours

vi. Head CT is strongly suggested if possible

8. Second tier therapy to be considered in salvageable patients **under conditions such as:**

a. To be considered in case of:

i. **Persistent neuroworsening not responding to an increased therapeutic intensity level (as indicated above). CT is recommended, if possible.**

ii. **Follow-up CT (eg day 5 CT) showing Inadequate response to treatment such as persistent edema**

b. Primary options

i. Decompressive craniectomy

ii. High dose IV barbiturates:

1. **Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion (approx. 4-6 gm/day)**

2. **Hypotension must be avoided**

c. Other options

i. Hyperventilation to maintain PaCO2 25-30 mmHg (PaCO2 22-28 mmHg in Cochabamba), use for shortest time period possible to reverse neurological deterioration

ii. Hypothermia

iii. Lund therapy

9. Management following decompressive craniectomy

a. Use adequate sedation and analgesia

b. Mild hyperventilation to maintain PaCO2 30-35 mmHg (PaCO2 28-32 mmHg in Cochabamba)

c. Hyperosmolar/hypertonic therapy

i. Use after sedation/analgesia is optimized

ii. Mannitol should be used first, except in the following situations (HHH):

a. Arterial Hypotension

b. Hypovolemia

c. Hyponatremia

2. Mannitol therapy guidelines and dosing

a. Plasma osmolarity **or tonicity** should be monitored at least every 12-**24** hours

b. Plasma osmolarity **or tonicity** should be calculated using the following formulae:

1. Osmolarity = 2 * (Na) + (BUN/ 2.8) + (Glucose/18)

2. **Tonicity = 2 * (Na + K) + (Glucose/18)**

ii. Hyperosmolar (Mannitol) therapy should be suspended for plasma osmolarity > 320 **or tonicity > 340**

c. Continue the pre-operative mannitol dosing regimen using 20% Mannitol bolus:

i. 100ml (20gm) IV every 3-4 hours for the first 3 days, then

ii. 80ml (16gm) IV every 3-4 hours on day 4, then

iii. 60ml (12gm) IV every 3-4 hours on day 5, then

iv. 40ml (8gm) IV every 3-4 hours on day 6 and suspend

3. Hypertonic saline therapy guidelines and dosing

a. Hypertonic saline should only be used in cases of HHH as described above

b. Plasma osmolarity **or tonicity** and serum sodium should be monitored at least every 12-**24** hours

i. Plasma osmolarity **or tonicity** should be calculated using the following formulae:

a. Osmolarity = 2 * (Na) + (BUN/ 2.8) + (Glucose/18)

b. **Tonicity = 2 * (Na + K) + (Glucose/18)**

2. **Hypertonic saline therapy should be suspended for plasma osmolarity > 360 or tonicity > 380 or serum sodium > 160**

c. Continue the pre-operative hypertonic saline dosing regimen using 5%NaCl solution bolus:

i. 80ml normal saline (0.9%NaCl) + 20ml 20%NaCl = 100ml 5%NaCl solution

ii. 100ml IV every 4-12 hours for 6 days then suspend

d. High dose IV barbiturates

i. Use after hyperventilation and hyperosmolar/hypertonic therapies

1. Dosing: Thiopental (Pentothal) 2.5-4 mg/kg/hr IV continuous infusion for 3 days

2. Hypotension must be avoided

e. Obtain head CT within 24 hours following decompressive craniectomy

i. If edema improved, stop sedation, hyperventilation, hyperosmolar/hypertonic therapy, and high dose barbiturate therapy and evaluate neurologic exam and GCS

ii. If edema not improved or worse, continue sedation, hyperventilation, hyperosmolar/hypertonic therapy, and high dose barbiturate therapy as above

10. Contraindicated treatments

a. Corticosteroids for brain injury treatment

b. **Use of anticonvulsants for prophylaxis of late epilepsy (beyond 28 days)**

Definitions

Neuroworsening[1] was defined as a decrease in GCS motor score by ≥2 points, deterioration in pupillary reactivity, development of anisocoria of ≥2 mm, a new focal motor defect, or evidence of rostrocaudal deterioration.

Pupil reactivity was considered normal when both pupils were reactive, abnormal when at least 1 was non-reactive, and unknown when at least 1 was unknown and any tested pupils were reactive.

First CT was classified according to the Marshall classification[2].

Table S1. Marshall Classification of CT A mass lesion is considered evacuated if it was subsequently evacuated.

Category	Definition
Diffuse injury I (no visible pathology)	No visible intracranial pathology seen on CT scan
Diffuse injury II	Cisterns are present with midline shift of 0–5 mm and/or: lesion densities present; no high- or mixed-density lesion > 25 cc; may include bone fragments and foreign bodies
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift 0–5 mm, no high- or mixed-density lesion > 25 cc
Diffuse injury IV	Midline shift > 5 mm, no high- or mixed-density lesion > 25 cc
Evacuated mass lesion	Any lesion surgically evacuated
Non-evacuated mass lesion	High- or mixed-density lesion > 25 cc, not surgically evacuated

Gehan rank is a way of ordering times that accounts for right censoring. It equals the number of participants whose survival time is definitely lower minus the number whose survival time is definitely higher. The survival time for person A is definitely higher than that for person B if person B has died and

the time until death for person B is less than the time of death for person A or less than or equal to the time of censoring for person A. The survival time for person A is definitely lower than that for person B if person A has died and the time until death for person A is less than the time of death for person B or less than or equal to the time of censoring for person B.

Outcome measures

Table S2 shows the measures, the score used, the range, the direction of scoring, and the descriptive shown in the outcome tables.

Table S2 – Description of outcome measures

Measure	Score	Range	Direction of scoring	Descriptive shown
Primary Outcome				
21-Item Composite	Average percentile	0 to 100	Higher is better	Median (25^{th} %ile, 75^{th} %ile)
Individual Measures in Composite				
1 Survival time	Gehan rank	-323 to 323	Higher is better	Median (25^{th} %ile, 75^{th} %ile) from Kaplan-Meier curve
2 Time to Following Commands (Days)	Gehan rank	-323 to 323	Lower is better	Median (25^{th} %ile, 75^{th} %ile) from Kaplan-Meier curve
3 GOAT at Discharge	Sum of errors on the orientation questions	0 to 78	Lower is better	Median (25^{th} %ile, 75^{th} %ile)
Assessments at 3-Month				
4 GOAT	Sum of errors on the orientation questions	0 to 78	Lower is better	Median (25^{th} %ile, 75^{th} %ile)

5 DRS	Sum of eye opening, communication ability, and motor response scores	0 to 12	Lower is better	Median (25th %ile, 75th %ile)
6 GOS-E	Score	1 to 8	Higher is better	Median (25th %ile, 75th %ile)
Assessments at 6-Month				
7 GOAT	Sum of errors on the orientation questions	0 to 78	Lower is better	Median (25th %ile, 75th %ile)
8 DRS	Sum of eye opening, communication ability, and motor response scores	0 to 12	Lower is better	Median (25th %ile, 75th %ile)
9 GOS-E	Score	1 to 8	Higher is better	Median (25th %ile, 75th %ile)
Neuropsychological Measures				
10 Mini-Mental Status Exam	Number correct†	0 to 30	Higher is better	Median (25th %ile, 75th %ile)
11 Spanish Verbal Learning Test	Total Learning Score†	0 to 80	Higher is better	Median (25th %ile, 75th %ile)
12 Spanish Verbal Learning Test	Long Delay Free Recall†	0 to 16	Higher is better	Median (25th %ile, 75th %ile)
13 Brief VisuoSpatial Memory Test (0-36)	Total Learning†	0 to 36	Higher is better	Median (25th %ile, 75th %ile)

14 Brief VisuoSpatial Memory Test	Delayed Recall†	0 to 12	Higher is better	Median (25th %ile, 75th %ile)
15 WAIS III Digit Symbol	Raw score†	0 to 133	Higher is better	Median (25th %ile, 75th %ile)
16 WAIS III Symbol Search	Raw score†	0 to 60	Higher is better	Median (25th %ile, 75th %ile)
17.1* Grooved Pegboard - Dominant Hand	Time to complete (Seconds)†	Up to 301	Lower is better	Median (25th %ile, 75th %ile)
17.2* Grooved Pegboard - Non-Dominant Hand	Time to complete (Seconds)†	Up to 301	Lower is better	Median (25th %ile, 75th %ile)
18.1* Trails A	Time to complete (Seconds)†	Up to 96	Lower is better	Median (25th %ile, 75th %ile)
18.2* Color Trails #1	Time to complete (Seconds)†	Up to 241	Lower is better	Median (25th %ile, 75th %ile)
19 Color Trails #2	Time to complete (Seconds)†	Up to 241	Lower is better	Median (25th %ile, 75th %ile)
20.1* COWAT	Number of words†	0 to 99	Higher is better	Median (25th %ile, 75th %ile)
20.2* Category Fluency - Animals	Number of words†	0 to 99	Higher is better	Median (25th %ile, 75th %ile)
20.3* Category Fluency - Actions	Number of words†	0 to 99	Higher is better	Median (25th %ile, 75th %ile)
21 PASAT	Number correct†	0 to 49	Higher is better	Median (25th %ile, 75th %ile)
Measures not in the composite				

14 day cumulative mortality	Kaplan-Meier estimate at 14 days	0 to 100%	Lower is better	% +/- Standard error
6 month cumulative mortality	Kaplan-Meier estimate at 6 months	0 to 100%	Lower is better	% +/- Standard error
GOS-E categories	Category	1 to 8	Higher is better	n (%)
Protocol-specified secondary outcomes				
ICU length of stay	Days	1 to 185	Lower is better	Median (25^{th} %ile, 75^{th} %ile)
ICU length of stay with brain-specific treatment	Days	1 to 185	Lower is better	Median (25^{th} %ile, 75^{th} %ile)
Individual complications	Number with complication	0 to 324	Lower is better	n (%)
Non-protocol-specified outcomes				
Integrated Brain-Specific Treatment Intensity	Treatment-hours	0 and up	Lower is better	Median (25^{th} %ile, 75^{th} %ile)
Individual treatments	% of participants (average number of hours per participant getting that treatment)	0 to 100 (0 and up)	No clear directionality	
Other lengths of stay, ventilator days	Days	1 to 185	Lower is better	Median (25^{th} %ile, 75^{th} %ile)
% of readings meeting description	%	0 to 100	Lower is better	Median (25^{th} %ile, 75^{th} %ile), Mean (sd)

[†]Difference between the observed score and that predicted from regression on age, sex, and education was used as the element for the composite. Descriptives are for the scores indicated, not the residuals.

*Individual measures numbered with a decimal attachment (17.1, 17.2, 18.1, etc.) were combined into a subcomposite before being entered into the composite. Thus composite index 17 is a composite of the two Grooved Pegboard scores.

The primary outcome is a composite of 21 elements. For the primary outcome, the subject's percentile was determined for each element separately and their score is the average of these percentiles over the 21 elements (range 0-100, lower percentiles represent worse outcomes).The percentile is defined as the percent of patients in the trial with worse scores plus half the percent with equal scores. Before determining percentiles, the neuropsychological test scores (from tested patients only, i.e. excluding deaths and those too neurologically impaired to take the test) were regressed on age, sex, and years of education to reduce variability and the percentiles are based on residuals, i.e. the difference between the observed and regression-predicted score. In determining the percentiles, deaths are not considered to be missing data for measures assessed after the time of death but are assigned a psuedoscore worse than the lowest score or residual and, for neuropsychological test scores, those too neurologically impaired to take the test are assigned a psuedoscore better than those who died but worse than the lowest residual. Percentiles are averaged across measures for each individual.

Missing data on some measures is dealt with by using average of the individual's observed percentiles. (Assigned pseudoscores on neuropsychological measures for death or untestability due to neurological impairment are considered observed, not as missing data.) This assumes that the percentiles on the observed measures are a reasonable proxy for the percentiles on the missing measures. Percentiles are used rather than the ranks (which were used in the paper on which the composite outcome was based[3]) because they are equivalent if no measures have missing data. Furthermore, the ranks on a measure depend on the number of cases with missing data which is not relevant to the level of functioning. As an example, suppose there are 100 cases and 2 measures. On the first measure, all 100 cases have scores and the ranks go from 1 to

100. On the second measure, 20 cases are missing scores so the remaining 80 have ranks from 1 to 80. Now suppose someone has the best score on one measure and is missing the other. If the ranks are used, the person has an average rank of 80 if the first measure is missing and an average rank of 100 if the second measure is missing. This is not desirable. One would want the composite to reflect their excellent performance regardless of which measure is missing. Using the percentiles, the highest score has a percentile of 99.5 on the first measure and 99.4 on the second measure, and a nearly identical average composite regardless of which measure is missing.

The outcome variables in the primary composite are:

- Mortality
- Time to follow commands (measured as time from injury to following simple commands as defined by a score of 6 on the motor scale of the GCS)
- Sum of Errors on orientation questions in the GOAT[4]
- Functional status at 3 and 6 months
- Neuropsychological assessment (Table 1).

Functional Status: The Disability Rating Scale (DRS), and the Glasgow Outcome Scale Extended (GOS-E) are used to measure functioning level in everyday life. The DRS[5] is a brief measure of impairment, disability and participation. Only the assessment of eye opening, communication ability and motor response are used in the analysis. The GOS-E[6] is the most commonly used measure of functional outcome in traumatic brain injury. This measure is the extension of the original Glasgow Outcome Scale, developed to address limitations with the

original measure including unreliability and insensitivity to change. They have been translated and used in previous research in Latin America by this research group.

Neuropsychological Test Battery: A battery of measures that examines important neuropsychological constructs which are sensitive to the integrity of brain functions, including traumatic brain injury, are used. The selection of the neuropsychological outcome measures was based on the University of Washington investigators' prior work with TBI, the recommendations from the NINDS conference addressing outcome measurement in clinical trials involving moderate or severe traumatic brain injury[7], and the measures selected for the Traumatic Brain Injury Clinical Trials Network of the National Center for Medical Rehabilitation Research. These are widely used published instruments with considerable psychometric work. In addition, through the international work of Drs. Robert Heaton and Mariana Cherner, these measures have been translated, adapted and normed on monolingual Spanish speakers in the US border region. In choosing the measures, considerations were also given so that: 1) they cover different aspects of functioning that are clinically relevant and likely to be affected by head injury; 2) the measures possess good psychometric properties with respect to sensitivity, validity, and reliability, and 3) the measures are appropriate for use with a broad spectrum of head injury severity and likely to be responsive to treatment effects directed at improving outcome. Tests of a variety of cognitive functions are included because head injury can impact any or all of the functions depending upon severity. The areas assessed are clinically relevant because they are prevalent and a major cause of disabilities in this population after the acute stage of injury.

The neuropsychological domains and the measures used to examine them are:

Mental Status (Mini-Mental State Examination[8,9]);

Working Memory (Paced Auditory Serial Addition Test [PASAT]- first subtest [10]);

Speed of Information Processing (WAIS III Digit Symbol, and Symbol Search subtests, Color Trails part 1, Trail Making Test Part A [9,11-13]);

Learning and Recall **(**Spanish Verbal Learning Test; Brief Visuospatial Memory Test Revised[9,14-16]);

Executive Functioning (Noun Fluency (animals)[17], Verbal Fluency (actions)[18]; *Controlled Oral Word Association Test (COWAT PMR)[19],* Color Trails part 2 [9,13]);

Motor Speed & Dexterity **(**Grooved Pegboard Test[20]).

Scores used in the Composite measure include the MMSE total score, the Spanish Verbal Learning Test total learning score and Long Delay Free Recall, the Brief Visuospatial Memory Test Revised total learning number correct, and delay correct, WAIS III Digit Symbol and Symbol Search scores, Color Trails 2 time to completion, number correct on PASAT first subtest and three subcomposite scores where tests are grouped together to form 1 element to be entered into the composite. The first is Grooved Pegboard dominant and non-dominant times. The second subcomposite is composed of Color Trails 1 and Trail Making Test Part A times to completion. The third subcomposite is composed of total words correct on COWAT, Category Fluency Test for Animals and Category Fluency Test for Actions. As indicated above, residuals from regressions on age, sex, and education were used along with pseudo scores for deaths and those too neurologically impaired to take the test. Use of T-scores based on the norms for monolingual Spanish-speakers was considered, but uninjured Bolivians did not have scores with the expected mean of 50 and there was a substantial relationship between years of education and the T-scores for some measures.

Trained examiners blinded to assigned treatment administered the three- and six-month outcome measures in the participant's primary language. All measures were given if the participant's primary

language was Spanish. If the participant primarily spoke one of the indigenous languages (e.g. Quechua or Aymara), the functional status measures were given in that language and the neuropsychological measures were not given.

Rationale for the composite outcome

Severe traumatic brain injury affects many aspects of a person's life. It is highly desirable that a TBI treatment have a positive impact on all or most of the areas likely to be affected. The most commonly used outcome for TBI clinical trials is GOS or GOS-E, often dichotomized into favorable/unfavorable. While GOS-E has excellent validity, the dichotomous version requires about 800 cases to detect a 10 percentage point difference in the percent with favorable outcome. Even the full score compresses both the low and high end of functioning. Early indicators of brain function such as time to follow commands and functional outcomes at 3 months provide some additional spread as well as some information on level of functioning for those who would be lost to follow-up before 6 months. Neuropsychological test scores, while measuring cognitive impairments rather than everyday functioning, are more sensitive to brain injuries and have a much wider range for those toward the better end of the GOS-E score range. Furthermore, they are considered to be the major cause of disabilities in everyday functioning in TBI. Additionally, cognitive effects are considered to be some of the most direct effects of both the initial impact to the brain and the subsequent secondary insults. As indicated in the sample size section below, simulations bear out the increased sensitivity of the composite outcome, requiring only 324 cases to detect a comparable consistent effect in all measures.

The composite outcome as defined above implicitly weights each element equally. Since there are more cognitive measures, cognitive performance is highly influential in the composite. Note

that mortality is also highly influential because a participant who has died before an assessment is assigned the worst score on all the cognitive measures at that time. Note that although 14 day mortality and 6 month mortality (both based on the Kaplan-Meier estimates) are shown in the table of individual outcome measures, mortality is only one variable in the composite with the Gehan rank[21] used to account for censoring of cases lost to follow-up.

Protocol-specified secondary outcomes are:

ICU length of stay, ICU length of stay while receiving brain-specific treatments

Systemic complications

29 complications were specifically tracked in addition to 'other' complications. They are below. Those from 'death' on are considered systemic complications. Protocol-specified complications of interest were major respiratory problems, sepsis, decubitus ulcers, and any non-neurologic complication.

- ICP catheter related infection
- ICP monitoring system malfunction
- ICP catheter related hemorrhage
- CSF leak
- Cerebral abscess
- New or expanding lesion
- Ventriculitis
- Seizure
- Hydrocephalus
- Death
- Cardiac arrest
- Acute lung injury

- ARDS
- Sepsis
- Septic shock
- Coagulopathy
- Nosocomial pneumonia
- Community-acquired pneumonia
- Wound infection
- Decubitus ulcers
- Pulmonary thromboembolism
- Deep vein thrombosis
- Acute renal Failure
- Urinary infection
- Gastrointestinal hemorrhage
- Hyponatremia (< 135)
- Hypernatremia (> 145 meq)
- Other water and ionic disorders

Other secondary outcomes are:

Hospital length of stay

Ventilator days

Use of high-dose barbiturates

Decompressive craniectomy

Therapeutic intensity — Intensity of therapy for treatment of intracranial hypertension was recorded hourly during active treatment in the emergency department or ICU. We tracked eleven

therapies for intracranial hypertension. These were mechanical ventilation, sedation, analgesia, paralytics, mannitol, hypertonic saline, CSF drainage, furosemide, pressors, high dose barbiturates, hyperventilation. Mannitol and hypertonic saline were coded as 1 if they were given once in that hour and as 2 if given multiple times. Hyperventilation was coded as 1 if the person was hyperventilated to reach a PaCO2 between 30 and 35 mm Hg (28 to 32 at high altitude) and coded as 2 if the targeted PaCO2 was 29 or less (27 or less at high altitude). An intervention coded as 2 was counted as 2 interventions for that hour, yielding a possible hourly intensity between 0 and 14. Interventions were to be recorded only if they were done because of the brain condition. Because mechanical ventilation, sedation, and analgesia were routinely used in the ICU for many reasons and it was often not clear why it was given in an hour, we considered the other 8 to be more indicative of the intensity of effort to minimize intracranial hypertension. We called the remaining 8 interventions brain-specific treatments (BT), with hourly brain-specific treatment between 0 and 11. We summed the hourly intensities over the time of recording to get the integrated treatment intensity and similarly for the hourly brain-specific intensities to get the integrated brain-specific treatment intensity.

ICP, CPP, and vital signs were recorded hourly while the patient was in the ICU. These are summarized by the number of readings in the range specified and the percent of readings in that range.

Brain-Specific Therapeutic Interventions	**Code**
Mannitol – 1 dose/hour[1]	1
Mannitol – More than 1 dose in same hour[1]	2
Hypertonic saline – 1 dose/hour[1]	1

Hypertonic saline – More than 1 dose in same hour[1]	2
Hyperventilation to P_aCO_2 30 – 35 mm Hg[1]	1
Hyperventilation to P_aCO_2 < 30 mm Hg[1]	2
Neuromuscular blockade	1
Cerebrospinal fluid drainage	1
Furosemide	1
Pressors	1
High dose barbiturates	1

[1]Mannitol, hypertonic saline, and hyperventilation scored as 1 or 2, depending on number or degree of treatments each hour.

Example of calculation of the composite

To calculate the composite, first note the scores for each element for each participant and whether higher or lower scores are better. For this example, there are 6 elements in the composite and 5 participants. Each participant's survival information is also shown.

Table S3a Table of scores used in the example of calculating the composite

Measure Element Participant	Survival	GOS-E 3-mo Element 1 Higher is better	DRS 3-mo Element 2 Lower is better	GOS-E 6 mo Element 3 Higher is better	Mini-mental exam Element 4 Higher is better	Trails A Element 5 Lower is better	PASAT Element 6 Higher is better
1	alive at 180 days	7	0	8	30	missing	35
2	alive at 90 days, then lost to follow-up	6	0	missing	missing	missing	missing
3	died at 5 days	1	dead	1	dead	dead	dead
4	alive at 180 days	3	3	3	untestable	untestable	untestable
5	died at 120 days	3	8	1	dead	dead	dead

Then calculate the percentile (percent worse) for each of the elements, keeping in mind the direction of scoring. Count each person with a value on that element equal to that of the participant as half a person being worse. To get the value of composite for each participant, sum their percentiles and divide by the number of non-missing elements.

Table S3b. Percentiles on each element and the composite for the example

Percentile[1]							Composite[2]
Participant	Element 1	Element 2	Element 3	Element 4	Element 5	Element 6	
1	90	80	88	88	missing	88	87
2	70	80	missing	missing	missing	missing	75
3	10	10	25	25	33	25	20
4	40	50	62	62	83	62	60
5	40	30	25	25	33	25	30

[1]Percentile=100*(number worse+.5*number equal on this element)/number not missing on this element[2]Composite=average percentile=(sum of percentiles for this participant)/(number of non-missing percentiles for this participant)

Sample size, data quality and monitoring, randomization, data analysis

Sample size

The sample size was determined by simulation to provide 80% power to detect a 10-percentage point increase in the percent with good outcome or moderate disability on the GOS-E (from 51.4% to 61.4% based on the observed percent in that category among the severely injured cases in the Magnesium Sulfate trial[22], corresponding to an odds ratio of 1.5), and a corresponding improvement on other measures (defined as the same difference in the logistic parameter for other cut points on the GOS-E and other categorical outcomes and the same percent reduction in deficit for continuous outcomes. Reduction in deficit is determined by examining the scores of TBI cases and non-TBI controls. For example, for severe TBI, say 62% of cases have unfavorable outcome on the GOS and 2% of controls do. Then the deficit is 60 percentage points, i.e. 62%-2% and a 10 percentage point treatment effect reflects a 17%(=10 points/60 points) reduction in deficit. If the average score on IQ is 80 for those with severe TBI and 110 for controls, the deficit is 30 points and a treatment effect of 5 points (=17%*30 points of deficit) on average on IQ would be considered equivalent to the 10 percentage point effect on the dichotomized GOS-E.). Since we had no comprehensive individual data using the proposed battery, we performed the simulation using data on analogous measures from the Magnesium Sulfate trial[22]. One blinded interim efficacy analysis was conducted when half the subjects completed their 6-month assessment. There was no interim futility analysis as we felt the narrowest confidence interval would be important if ICP monitoring was not shown to be superior. The study was not designed to have high power to detect an effect on a single (non-composite) measure. With 324 cases, the study would have only 40% power to detect a 10 percentage point difference in the percent in the favorable categories on the GOS-E.

Data quality and monitoring

Inter-rater-reliability analyses were conducted for the abbreviated injury scale (AIS), GCS, CT scan interpretations (coded according to Marshall et al)[2], GOS-E, and GOAT. Quality of acute-care data was monitored monthly until achieving an error rate of <1%. Outcome data were checked and double-scored for accuracy; questions were discussed monthly with the outcome monitor. We performed double entry and utilized electronic data checks to ensure accuracy. See Carney et al, 2012 for details[23].

Randomization

Randomization sequences were computer generated by a data center biostatistician (JB) and stratified on site, severity (GCS 3-5 or Motor 1-2 if intubated vs. GCS 6-8 or Motor 3-5 if intubated) and age (<40 vs. ≥40), and blocked with block size 2 or 4. That is, within each site, severity, age group combination, the randomization was restricted so that number of participants assigned to each treatment was forced to be exactly equal after every 2 or 4 assignments in that strata. Sequences were encoded in password-protected Access databases sent to the sites. After obtaining consent, the study coordinator at the site entered the subject number and stratification information into the Access program, which returned the assignment. If the laptop could not be used, the coordinator phoned a study monitor at the Latin America Coordinating Center who flipped a coin and told the coordinator the treatment assigned.

Data Analysis

The study is a superiority trial, designed to determine whether either treatment shows reliable evidence of better outcome. It was not designed as an equivalence or non-inferiority trial. Thus the null hypothesis is that there is no difference in outcomes between management groups. This hypothesis is tested by comparing the two groups on the primary composite[3] using a blocked

Wilcoxon test[24] comparing the average percentiles for people in the two treatment groups after controlling for center, TBI severity group and age group. A 2-sided .05 significance level is used. Primary analysis is according to the intention-to-treat principle, i.e., all randomized cases are followed and included with their assigned treatment group regardless of the management protocol actually used. To supplement the composite test of the overall hypothesis, individual measures are summarized for each group. An odds ratio with a confidence interval is calculated for each outcome based on proportional odds regression[25]. The regressions account for the stratification variables (site, age group, and severity group). Proportional odds regression can be thought of as performing a logistic regression on the outcome dichotomized at each possible value of that outcome. The method assumes that the odds ratio has the same true value for all such dichotomizations and combines the results in a way that legitimately accounts for the fact that the same cases are in the logistic regression for each dichotomization.

The data analyses were performed by JB and NT, using SPSS and SAS.

Rationale for the primary analysis method.

The composite outcome is sensitive to treatments for which the direction of the effect is the same on each component measure. That is what we would expect if one management protocol were more effective than the other. The method of analysis requires few assumptions about the distribution of the individual measures making up the composite or the intercorrelation among them. With the complicating factors of deaths and untestability, the distributions are far from the bell-shape of the normal distribution, making methods based on the normal distribution unwarranted. This also made shift alternatives (moving the entire distribution, for example by adding the same value to each observation) inappropriate for summarizing the treatment effect—a treatment is not likely to make everyone who would have died a little less dead if they were in the control arm. Thus we used the odds ratio based on a logistic proportional odds model (i.e. one that assumes the odds of a poor outcome are the same for all possible points of dichotomization for the scores) to summarize the treatment effect.

Authorship Responsibilities

	Study design	Site & personnel training	National & International logistics	Data collection & oversight	Data analysis and interpretation	Vouches for data & analysis	Wrote first draft	Wrote paper *	Decided to publish paper
Randall M. Chesnut, MD	X				X	X	X	X	X
Nancy Temkin, PhD	X				X	X	X	X	X
Nancy Carney, PhD	X	X	X	X	X	X		X	X
Sureyya Dikmen, PhD	X	X		X	X	X		X	X
Carlos Rondina, MD	X	X	X		X	X		X	X
Walter Videtta, MD	X	X	X		X			X	X
Gustavo Petroni, MD	X	X		X	X			X	X
Silvia Lujan, MD	X	X		X	X			X	X
Jim Pridgeon			X					X	X

, MHA									
Jason Barber, MS		X			X	X		X	
Joan Machamer, MA		X		X		X		X	
Kelley Chaddock, BA			X					X	
Juanita M. Celix, MD		X							
Mariann a Cherner, PhD	X	X		X					
Terence Hendrix		X	X	X					

* Majority of writing effort was accomplished in rewriting a first, rough draft, refining and performing data analyses, and iteratively editing a near-final draft at a team meeting dedicated to this purpose held over thee days in August in Rosario, Argentina.

CONSORT participant flow chart (Figure S1) Cases that were eligible but not randomized were somewhat younger, significantly more likely to be a pedestrian, arrived at the hospital more quickly, were more likely to have reactive pupils, and more likely to have a non-evacuated mass lesion on CT. There were no significant differences on baseline characteristics between those followed to death or 6 month outcome and those lost to follow-up before 6 months. See Table S4.

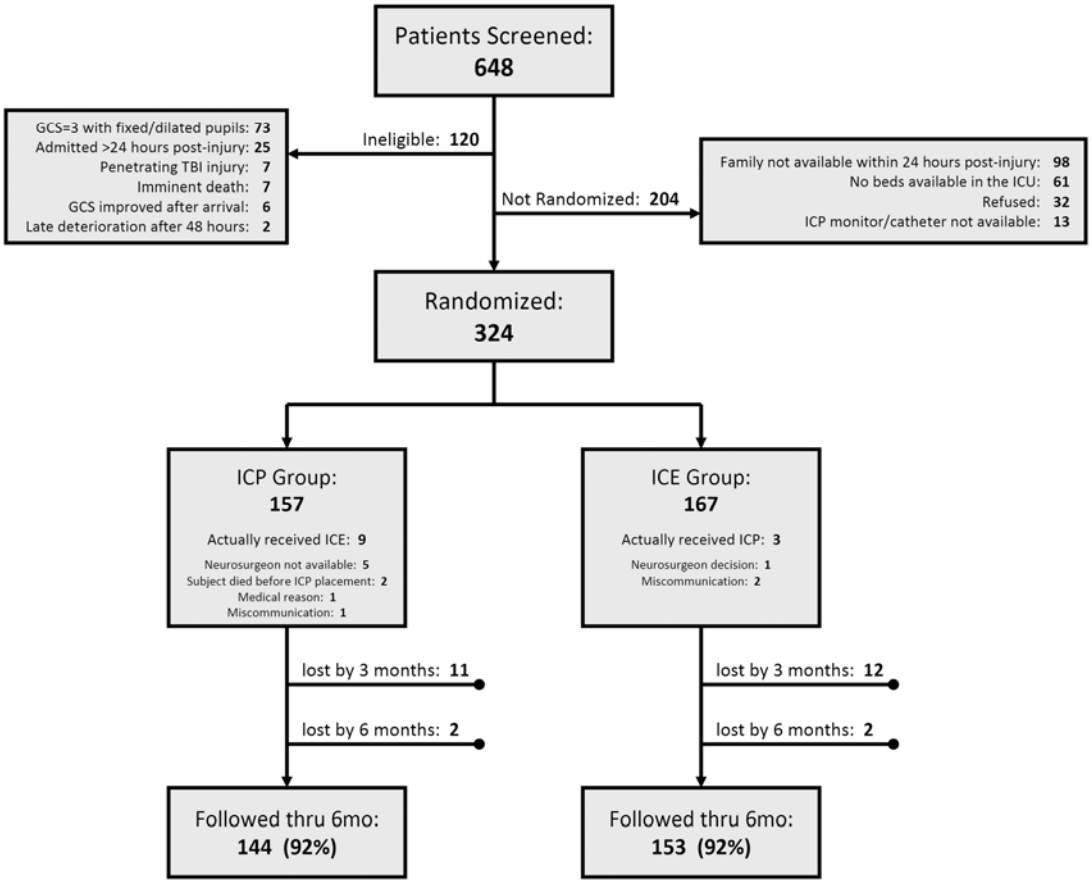


Table S4 - Demographics and Injury Characteristics, Split by Randomization and Six-Month Status

Category *	Eligible for RCT			Followed at 6 Months		
	Not Randomized	Randomized	P-value ±	No	Yes	P-value ±
N	**204**	**324**		**27**	**297**	
Age						
Median (IQR)	32.5 (23, 44)	29 (22, 44)	.25	28 (20, 38)	29 (22, 45)	.22
13-29	57 (38%)	164 (51%)	**.001**	15 (56%)	149 (50%)	.42
30-39	47 (31%)	56 (17%)		6 (22%)	50 (17%)	
40-59	29 (19%)	80 (25%)		6 (22%)	74 (25%)	
60+	17 (11%)	24 (7%)		0 (0%)	24 (8%)	
Unknown	54					
Sex						
Male	187 (92%)	283 (87%)	.15	24 (89%)	259 (87%)	1.00
Female	17 (8%)	41 (13%)		3 (11%)	38 (13%)	
Circumstances of Injury						

Category *	Eligible for RCT			Followed at 6 Months		
	Not Randomized	Randomized	P-value ±	No	Yes	P-value ±
Car	14 (9%)	44 (14%)	**.04**	1 (4%)	43 (15%)	.27
Motorcycle	42 (28%)	117 (37%)		10 (37%)	107 (37%)	
Bicycle	7 (5%)	13 (4%)		1 (4%)	12 (4%)	
Pedestrian	51 (34%)	68 (21%)		7 (26%)	61 (21%)	
Fall	20 (13%)	49 (15%)		6 (22%)	43 (15%)	
Assault	10 (7%)	21 (7%)		1 (4%)	20 (7%)	
Accidental strike	3 (2%)	3 (1%)		0 (0%)	3 (1%)	
Other	4 (3%)	2 (1%)		1 (4%)	1 (0%)	
Unknown	53	7		0	7	
Mode of Transport to Initial Hospital						
Ambulance	47 (41%)	85 (45%)	.54	7 (58%)	78 (44%)	.63
Taxi	17 (15%)	30 (16%)		1 (8%)	29 (16%)	
Firetruck	10 (9%)	23 (12%)		0 (0%)	23 (13%)	
Car	16 (14%)	23 (12%)		2 (17%)	21 (12%)	

Category *	Eligible for RCT			Followed at 6 Months		
	Not Randomized	Randomized	P-value ±	No	Yes	P-value ±
Other	24 (21%)	27 (14%)		2 (17%)	25 (14%)	
Unknown	90	136		15	121	
Admitted Directly to Study Hospital						
No	89 (52%)	198 (61%)	**.04**	21 (78%)	177 (60%)	.10
Yes	83 (48%)	125 (39%)		6 (22%)	119 (40%)	
Unknown	32	1		0	1	
Hours to Study Hospital *Median (IQR)*	1.8 (1.0, 5.5)	3.1 (1.0, 7.5)	**.008**	5.1 (1.5, 7.0)	3.0 (1.0, 7.6)	.23
Direct Admits *Median (IQR)*	1.0 (0.7, 2.3)	1.0 (0.5, 1.7)	.24	0.8 (0.4, 1.0)	1.0 (0.5, 2.0)	.26
Transfers *Median (IQR)*	3.7 (1.5, 6.5)	5.5 (3.0, 10.5)	**<.001**	5.6 (4.1, 9.0)	5.4 (2.9, 10.6)	.56
Time to First Hospital						
Transfers *Median (IQR)*	1.5 (0.5, 3.0)	2.7 (1.2, 6.5)	**<.001**	3.8 (1.6, 5.5)	2.5 (1.2, 6.5)	.58

Category *	Eligible for RCT			Followed at 6 Months		
	Not Randomized	Randomized	P-value ±	No	Yes	P-value ±
Randomized due to Late Deterioration						
No	---	245 (76%)	---	20 (77%)	225 (76%)	1.00
Yes	---	77 (24%)		6 (23%)	71 (24%)	
Unknown	---	2		1	1	
Hours to Randomization *Median (IQR)*	---	13.9 (8.1, 21.0)	---	18.1 (9.7, 23.3)	13.7 (8.0, 20.8)	.14
Qualified on early exam *Median (IQR)*	---	13.2 (7.5, 19.7)	---	15.1 (8.8, 20.6)	12.7 (7.4, 19.6)	.38
Qualified due to deterioration *Median (IQR)*	---	19.5 (10.7, 23.3)	---	22.0 (16.0, 31.1)	19.3 (10.7, 23.2)	.26
Randomization GCS Motor						
Median (IQR)	---	4 (3, 5)	---	5 (3, 5)	4 (3, 5)	.19
1 No response	---	9 (3%)	---	0 (0%)	9 (3%)	.43

Category *	Eligible for RCT			Followed at 6 Months		
	Not Randomized	Randomized	P-value ±	No	Yes	P-value ±
2 Extension to pain	---	42 (14%)		3 (13%)	39 (14%)	
3 Abnormal flexion to pain	---	41 (14%)		3 (13%)	38 (14%)	
4 Withdrawal to pain	---	62 (21%)		2 (9%)	60 (22%)	
5 Localizes to pain	---	148 (49%)		15 (65%)	133 (48%)	
6 Follows and obeys commands	---	0 (0%)		0 (0%)	0 (0%)	
Unknown	204	22		4	18	
First Pupil Reactivity in ICU						
Abnormal (at least 1 pupil)	13 (62%)	125 (44%)	.17	6 (27%)	119 (46%)	.12
Normal (both pupils)	8 (38%)	156 (56%)		16 (73%)	140 (54%)	
Unknown	183	43		5	38	
AIS Head Severity						
Median (IQR)	4 (3, 5)	5 (4, 5)	.29	5 (4, 5)	5 (4, 5)	.95
2	0 (0%)	1 (0%)	.54	0 (0%)	1 (0%)	1.00

Category *	Eligible for RCT			Followed at 6 Months		
	Not Randomized	Randomized	P-value ±	No	Yes	P-value ±
3	7 (28%)	59 (18%)		5 (19%)	54 (18%)	
4	7 (28%)	92 (29%)		8 (30%)	84 (28%)	
5	11 (44%)	170 (53%)		14 (52%)	156 (53%)	
Unknown	179	2		0	2	
Injury Severity Score (ISS)						
Median (IQR)	25 (16, 29)	25 (17, 27.5)	.40	25 (16, 30)	25 (17, 27)	.52
0-15	3 (12%)	42 (13%)	1.00	4 (15%)	38 (13%)	1.00
16+	22 (88%)	280 (87%)		23 (85%)	257 (87%)	
Unknown	179	2		0	2	
Marshall Classification first CT[2]						
1 - Diffuse Injury I	6 (4%)	1 (0%)	**<.001**	0 (0%)	1 (0%)	.26
2 - Diffuse Injury II	13 (9%)	44 (14%)		7 (27%)	37 (13%)	
3 - Diffuse Injury III	55 (39%)	138 (43%)		11 (42%)	127 (43%)	

Category *	Eligible for RCT			Followed at 6 Months		
	Not Randomized	Randomized	P-value ±	No	Yes	P-value ±
4 - Diffuse Injury IV	14 (10%)	22 (7%)		0 (0%)	22 (7%)	
5 - Evacuated Mass lesion	34 (24%)	106 (33%)		7 (27%)	99 (33%)	
6 - Not evacuated Mass Lesion	20 (14%)	11 (3%)		1 (4%)	10 (3%)	
Unknown	62	2		1	1	
Mesencephalic Cisterns first CT						
1 - Normal	20 (14%)	48 (15%)	.10	7 (27%)	41 (14%)	.19
2 - Compressed	57 (40%)	158 (49%)		10 (38%)	148 (50%)	
3 - Absent	66 (46%)	116 (36%)		9 (35%)	107 (36%)	
Unknown	61	2		1	1	
Midline Shift (≥5mm) first CT						
No	91 (65%)	204 (64%)	.83	21 (81%)	183 (62%)	.09
Yes	49 (35%)	117 (36%)		5 (19%)	112 (38%)	
Unknown	64	3		1	2	

Category *	Eligible for RCT			Followed at 6 Months		
	Not Randomized	Randomized	P-value ±	No	Yes	P-value ±
CT Signs of Intracranial Hypertension ∞						
No	1 (4%)	34 (11%)	.49	1 (4%)	33 (11%)	.34
Yes	23 (96%)	286 (89%)		24 (96%)	262 (89%)	
Unknown	180	4		2	2	

* Percentages exclude unknown values

± All tests of significance exclude the N/A and unknown categories. P-values on rows with a median and interquartile range are from Mann-Whitney U tests while those on the row for the first category are from Fisher exact tests.

∞ Impression of interpreting physician

Table S5 - Protocol Violations

	Overall	ICP	Imaging / Clinical Exam
N	324	157	167
Informed consent process			
Consent after randomization	5 (2%)	1 (1%)	4 (2%)
Consent not signed by LAR	0 (0%)	0 (0%)	0 (0%)
Invalid consent (not approved)	0 (0%)	0 (0%)	0 (0%)
Missing informed consent form	0 (0%)	0 (0%)	0 (0%)
Randomization			
Randomized ineligible case	0 (0%)	0 (0%)	0 (0%)
Didn't randomize eligible case	0 (0%)	0 (0%)	0 (0%)
Intervention			
ICP monitor in ICE patient	2 (1%)	---	2 (1%)
No ICP monitor in ICP patient without contraindication	6 (2%)	6 (4%)	---
Prematurely stopping monitor	0 (0%)	0 (0%)	---
Treatment			
No CT at admission	0 (0%)	0 (0%)	0 (0%)
TIL increase delayed —>1 hr	0 (0%)	0 (0%)	0 (0%)
Data management			
Unintentional loss of data	0 (0%)	0 (0%)	0 (0%)
Failure to report SAE	0 (0%)	0 (0%)	0 (0%)
Falsification of records or data	0 (0%)	0 (0%)	0 (0%)
Infringement of confidentiality	0 (0%)	0 (0%)	0 (0%)

	Overall	**ICP**	**Imaging / Clinical Exam**
N	324	157	167
Repeated or continuous negligence	0 (0%)	0 (0%)	0 (0%)

Table S6 - Demographics and Injury Characteristics No differences between treatment groups were significant at the 0.05 level[1].

Category [2]	**Total**	**ICP**	**Imaging / Clinical Exam**
N	**324**	**157**	**167**
Age			
Median (25th %ile, 75th %ile)	29 (22, 44)	29 (22, 44)	29 (22, 44)
13-29	164 (51%)	80 (51%)	84 (50%)
30-39	56 (17%)	27 (17%)	29 (17%)
40-59	80 (25%)	40 (25%)	40 (24%)
60+	24 (7%)	10 (6%)	14 (8%)
Sex			
Male	283 (87%)	143 (91%)	140 (84%)
Female	41 (13%)	14 (9%)	27 (16%)
Circumstances of Injury			
Car	44 (14%)	21 (13%)	23 (14%)
Motorcycle	117 (37%)	59 (38%)	58 (36%)
Bicycle	13 (4%)	6 (4%)	7 (4%)
Pedestrian	68 (21%)	38 (24%)	30 (19%)
Fall	49 (15%)	19 (12%)	30 (19%)

Category [2]	**Total**	**ICP**	**Imaging / Clinical Exam**
Assault	21 (7%)	10 (6%)	11 (7%)
Accidental strike	3 (1%)	2 (1%)	1 (1%)
Other	2 (1%)	1 (1%)	1 (1%)
Unknown	7	1	6
Mode of Transport to Initial Hospital			
Ambulance	85 (45%)	42 (46%)	43 (44%)
Taxi	30 (16%)	14 (15%)	16 (16%)
Firetruck	23 (12%)	10 (11%)	13 (13%)
Car	23 (12%)	11 (12%)	12 (12%)
6 - Other	27 (14%)	14 (15%)	13 (13%)
Unknown	136	66	70
Admitted Directly to Study Hospital			
No	198 (61%)	97 (62%)	101 (61%)
Yes	125 (39%)	60 (38%)	65 (39%)
Unknown	1		1
Hours to Study Hospital *Median (IQR)*	3.1 (1.0, 7.5)	3.5 (1.1, 8.3)	2.9 (1.0, 6.5)
Direct Admits *Median (IQR)*	1.0 (0.5, 1.7)	1.0 (0.5, 1.5)	1.0 (0.5, 2.0)
Transfers *Median (IQR)*	5.5 (3.0, 10.5)	6.3 (3.3, 12.2)	5.0 (2.8, 9.8)

Category [2]	**Total**	**ICP**	**Imaging / Clinical Exam**
Time to First Hospital			
Transfers *Median (IQR)*	2.7 (1.2, 6.5)	3.0 (1.1, 6.6)	2.5 (1.3, 6.3)
Randomized due to Late Deterioration			
No	245 (76%)	124 (79%)	121 (73%)
Yes	77 (24%)	32 (21%)	45 (27%)
Unknown	2	1	1
Hours to Randomization *Median (IQR)*	13.9 (8.1, 20.9)	13.5 (8.3, 20.5)	14.5 (8.0, 21.4)
Qualified on early exam *Median (IQR)*	13.2 (7.5, 19.6)	12.3 (7.5, 19.6)	14.0 (7.5, 19.7)
Qualified due to deterioration *Median (IQR)*	19.5 (10.7, 23.3)	20.2 (15.2, 23.3)	18.2 (9.4, 23.0)
Randomization GCS Motor			
Median (IQR)	4 (3, 5)	5 (3, 5)	4 (3, 5)
1	9 (3%)	3 (2%)	6 (4%)
2	42 (14%)	20 (14%)	22 (14%)
3	41 (14%)	19 (13%)	22 (14%)
4	62 (21%)	31 (21%)	31 (20%)
5	148 (49%)	73 (50%)	75 (48%)
6	0 (0%)	0 (0%)	0 (0%)
Unknown	22	11	11

Category [2]	Total	ICP	Imaging / Clinical Exam
First Pupil Reactivity in ICU			
Abnormal (at least 1 pupil)	125 (44%)	68 (49%)	57 (40%)
Normal (both pupils)	156 (56%)	70 (51%)	86 (60%)
Unknown	43	19	24
AIS Head Severity			
Median (IQR)	5 (4, 5)	5 (4, 5)	5 (4, 5)
2	1 (0%)	0 (0%)	1 (1%)
3	59 (18%)	32 (21%)	27 (16%)
4	92 (29%)	45 (29%)	47 (28%)
5	170 (53%)	79 (51%)	91 (55%)
Unknown	2	1	1
Injury Severity Score (ISS)			
Median (IQR)	25 (17, 28)	25 (16, 27)	25 (19, 29)
0-15	42 (13%)	23 (15%)	19 (11%)
16+	280 (87%)	133 (85%)	147 (89%)
Unknown	2	1	1
Marshall Classification first CT[2]			
Diffuse Injury I	1 (0%)	1 (1%)	0 (0%)
Diffuse Injury II	44 (14%)	24 (15%)	20 (12%)

Category [2]	**Total**	**ICP**	**Imaging / Clinical Exam**
Diffuse Injury III	138 (43%)	70 (45%)	68 (41%)
Diffuse Injury IV	22 (7%)	10 (6%)	12 (7%)
Evacuated Mass lesion	106 (33%)	48 (31%)	58 (35%)
Not evacuated Mass Lesion	11 (3%)	4 (3%)	7 (4%)
Unknown	2		2
Mesencephalic Cisterns first CT			
Normal	48 (15%)	26 (17%)	22 (13%)
Compressed	158 (49%)	77 (49%)	81 (49%)
Absent	116 (36%)	54 (34%)	62 (38%)
Unknown	2		2
Midline Shift (≥5mm) first CT			
No	204 (64%)	104 (66%)	100 (61%)
Yes	117 (36%)	53 (34%)	64 (39%)
Unknown	3		3
CT Signs of Intracranial Hypertension [3]			
No	34 (11%)	16 (10%)	18 (11%)
Yes	286 (89%)	140 (90%)	146 (89%)
Unknown	4	1	3

1 All tests of significance exclude the N/A and unknown categories. P-values on rows with a median and interquartile range are from Mann-Whitney U tests while those on the row for the first category are from Fisher exact tests. Interquartile range (IQR) is shown as the 25th %ile, 75th %ile.

2 Percentages exclude unknown values

3 Impression of interpreting physician

Table S7a – Outcomes for all randomized cases Odds ratios over 1 indicate better outcome in the ICP group. The study was designed to detect a difference corresponding to an odds ratio of 1.5.

Measure (range) [1]	**Total**	**ICP**	**Imaging / Clinical Exam**	**P Value** [2]	**Proportional Odds Ratio** [3]
N	324	157	167		
Followed at 6-Months	297 (92%)	144 (92%)	153 (92%)		
Primary Outcome					
21-Item Composite	55 (21, 76)	56 (22, 77)	53 (21, 76)	.49	1.09 (0.74, 1.58)
Individual Measures in Composite (Protocol-specified Comparisons)					
Survival Time(Days) [4]	>185 (12, >185)	>185 (34, >185)	>185 (8, >185)	.60[4]	1.10 (0.77, 1.57)
Days to Following Commands	26 (9, NEVER)	22 (9, NEVER)	27 (8, NEVER)	.59	1.13 (0.76, 1.68)
GOAT at Discharge	UNT (10, DEAD)	75 (9,DEAD)	UNT (11, DEAD)	.28	1.20 (0.81, 1.80)
3-Month Assessment N	296 (91%)	144 (92%)	152 (91%)		
GOAT	62.5 (1, DEAD)	32.5 (1, DEAD)	UNT (1, DEAD)	.30	1.24 (0.81, 1.91)
DRS *	1 (DEAD, 0)	1 (DEAD, 0)	2 (DEAD, 0)	.49	1.22 (0.76, 1.95)
GOS-E	3 (1, 6)	3 (1, 6)	3 (1, 6)	.66	1.21 (0.78, 1.86)
6-Month Assessment N	297 (92%)	144 (92%)	153 (92%)		

GOAT	49 (0, DEAD)	20.5 (0, DEAD)	76 (0, DEAD)	.41	1.21 (0.78, 1.88)
DRS	1 (DEAD, 0)	1 (DEAD, 0)	2 (DEAD, 0)	.69	1.18 (0.73, 1.91)
GOS-E	3 (1, 7)	3 (1, 7)	3 (1, 7)	.33	1.22 (0.79, 1.88)
1 - Death	123 (42%)	56 (39%)	67 (44%)	.33	
2 - Vegetative state	6 (2%)	3 (2%)	3 (2%)		
3 - Lower severe disability	28 (9%)	13 (9%)	15 (10%)		
4 - Upper severe disability	16 (5%)	8 (6%)	8 (5%)		
5 - Lower moderate disability	14 (5%)	7 (5%)	7 (5%)		
6 - Upper moderate disability	25 (8%)	12 (8%)	13 (8%)		
7 - Lower good recovery	35 (12%)	16 (11%)	19 (12%)		
8 - Upper good recovery	49 (17%)	28 (20%)	21 (14%)		
Neuropsychological Measures	286 (88%)	137 (87%)	149 (89%)		
Mini-Mental Status Exam	UNT (DEAD, 28)	UNT (DEAD, 29)	UNT (DEAD, 28)	.68	1.11 (0.72, 1.72)
Spanish Verbal Learning Test - Total Learning	UNT (DEAD, 36)	UNT (DEAD, 37)	UNT (DEAD, 34.5)	.94	1.01 (0.65, 1.56)
Spanish Verbal Learning Test - Long Delay Free Recall	UNT (DEAD, 8)	UNT (DEAD, 8)	UNT (DEAD, 8)	.63	0.94 (0.61, 1.46)
Brief VisuoSpatial Memory Test - Total Learning)	UNT (DEAD, 16.25)	UNT (DEAD, 18)	UNT (DEAD, 15)	.87	1.04 (0.67, 1.61)
Brief VisuoSpatial Memory Test - Delayed Recall	UNT (DEAD, 7)	UNT (DEAD, 7)	UNT (DEAD, 6)	.73	0.98 (0.63, 1.52)
WAIS III Digit Symbol	UNT (DEAD, 35)	UNT (DEAD, 33)	UNT (DEAD, 35)	.58	1.13 (0.73, 1.76)
WAIS III Symbol Search	UNT (DEAD, 13)	UNT (DEAD, 16)	UNT (DEAD, 12)	.31	1.29 (0.83, 2.00)
Grooved Pegboard - Dominant Hand	UNT (91, DEAD)	UNT (86.5, DEAD)	UNT (98.5, DEAD)	.69	1.14 (0.73, 1.77)

Grooved Pegboard - Non-Dominant Hand	UNT (102, DEAD)	UNT (98.5, DEAD)	UNT (114, DEAD)	.56	1.14 (0.73, 1.77)
Trails A	UNT (70, DEAD)	UNT (61, DEAD)	UNT (83, DEAD)	.52	1.16 (0.75, 1.80)
Color Trails #1	UNT (78, DEAD)	UNT (73, DEAD)	UNT (88.75, DEAD)	.47	1.22 (0.78, 1.89)
Color Trails #2	UNT (135, DEAD)	UNT (131, DEAD)	UNT (156, DEAD)	.41	1.25 (0.80, 1.94)
COWAT	UNT (DEAD, 22)	UNT (DEAD, 22.25)	UNT (DEAD, 22)	.94	1.01 (0.65, 1.57)
Category Fluency - Animals	UNT (DEAD, 13)	UNT (DEAD, 14)	UNT (DEAD, 13)	.62	1.13 (0.73, 1.75)
Category Fluency - Actions	UNT (DEAD, 8)	UNT (DEAD, 7.25)	UNT (DEAD, 8)	.96	1.05 (0.68, 1.62)
PASAT	UNT (DEAD, 18)	UNT (DEAD, 19)	UNT (DEAD, 17.75)	.40	1.21 (0.77, 1.90)
Post-hoc Comparisons					
14-Day Cumulative Mortality [4]	26%	21%	30%	.18 [4]	1.36 (0.87, 2.11)
6-Month Cumulative Mortality[4]	40%	39%	41%	.60 [4]	1.10 (0.77, 1.57)
Sensitivity analyses--Composite					
Actual Treatment Received	55 (21, 76)	57 (22, 76)	52 (21, 76)	.21	1.20 (0.82, 1.75)
Survivors Only	73 (58, 80)	73 (59, 80)	73 (59, 80)	.96	1.00 (0.61, 1.61)

1 Cells report the Median (25th %ile, 75th %ile) unless otherwise noted. All neuropsychological scores are raw performance scores rather than scaled scores. "UNT" means untestable due to severity of CNS impairment..

2 Statistical significance by blocked Wilcoxon[21,24] stratifying on site and age/severity from the randomization

3 Proportional odds ratio reported with 95% confidence interval, adjusting for site and age/severity from the randomization. A value >1 indicates a better disposition for the ICP group

4 Statistical significance and 95% confidence interval by Cox Model regression adjusting for site and age/severity from the randomization. Hazard ratio instead of odds ratio.

Table S7b - Outcomes, Survivors Only Odds ratios over 1 indicate better outcome in the ICP group. The study was designed to detect a difference corresponding to an odds ratio of 1.5. All comparisons of survivors are post hoc.

Measure [1]	**Total**	**ICP**	**Imaging / Clinical Exam**	**P Value** [2]	**Proportional Odds Ratio** [3]
N	**200**	**100**	**100**		
Followed at 6-Months	**173 (87%)**	**87 (87%)**	**86 (86%)**		
Primary Outcome					
21-Item Composite	73 (58 , 80)	73 (59, 80)	73 (59, 80)	.96	1.09 (0.74, 1.58)
Individual Measures in Composite					
Days to Following Commands	12 (6, 22)	11 (6, 21)	12 (5, 22)	.68	0.97 (0.60, 1.56)
GOAT at Discharge	16 (5, 78)	16 (5, 63.5)	16 (5, UNT)	.56	1.15 (0.70, 1.90)
3-Month Assessment N	**172 (86%)**	**87 (87%)**	**85 (85%)**		
GOAT	1 (0. 21)	1 (0, 21)	1 (0, 25)	.76	1.03 (0.59, 1.80)
DRS *	0 (0, 0.5)	0 (0, 0)	0 (0, 1)	.74	1.06 (0.51, 2.24)
GOS-E	6 (3, 7)	6 (4, 7.75)	6 (3, 7)	.60	1.10 (0.64, 1.90)
6-Month Assessment N	**173 (87%)**	**87 (87%)**	**86 (86%)**		
GOAT	1 (0, 11)	1 (0, 10.5)	1 (0, 11.3)	.71	1.15 (0.65, 2.04)
DRS *	0 (0, 0)	0 (0, 0)	0 (0, 0)	.49	1.28 (0.55, 2.96)
GOS-E	6 (4, 8)	7 (4, 8)	6 (4, 7)	.48	1.27 (0.74, 2.19)

1 - Death	0 (0%)	0 (0%)	0 (0%)	.95 [4]	
2 - Vegetative state	5 (3%)	2 (2%)	3 (3%)		
3 - Lower severe disability	28 (16%)	13 (15%)	15 (17%)		
4 - Upper severe disability	16 (9%)	8 (9%)	8 (9%)		
5 - Lower moderate disability	14 (8%)	7 (8%)	7 (8%)		
6 - Upper moderate disability	25 (15%)	12 (14%)	13 (15%)		
7 - Lower good recovery	35 (20%)	16 (19%)	19 (22%)		
8 - Upper good recovery	49 (28%)	28 (33%)	21 (24%)		
Neuropsychological Measures	**162 (81%)**	**80 (80%)**	**82 (82%)**		
Mini-Mental Status Exam	28 (22.25, 29)	28 (23.75, 29)	27 (22, 29)	.80	0.98 (0.57, 1.68)
Spanish Verbal Learning Test - Total Learning	34 (18, 42)	34 (18.5, 42)	33 (18, 42)	.41	0.76 (0.44, 1.31)
Spanish Verbal Learning Test - Long Delay Free Recall	7 (2, 10)	7 (2, 9)	7 (2, 10)	.06	0.64 (0.37, 1.11)
Brief Visuo Spatial Memory Test - Total Learning	15 (6.75, 21)	16 (7.75, 21)	14 (5.75, 21.25)	.37	0.78 (0.45, 1.37)
Brief Visuo Spatial Memory Test - Delayed Recall	6 (2, 10)	7 (2, 10)	6 (2, 9.25)	.15	0.72 (0.41, 1.26)
WAIS III Digit Symbol	32 (13.25, 45.75)	31 (16.5, 47)	33.5 (9.25, 45)	.86	0.96 (0.56, 1.68)
WAIS III Symbol Search	12 (3.5, 19.5)	13.5 (4.75, 20.25)	11 (1, 18)	.52	1.30 (0.75, 2.25)
Grooved Pegboard - Dominant Hand	99 (76, 210)	90 (74, 148)	105 (77.5, 281.5)	.83	1.07 (0.62, 1.86)

Grooved Pegboard - Non-Dominant Hand	107 (89, 285.25)	101 (86, 164.25)	119 (90.5, 301)	.96	1.03 (0.59, 1.80)
Trails A	77.5 (49.75, 96)	67 (47.75, 96)	90 (52, 96)	.88	1.04 (0.60, 1.80)
Color Trails #1	81 (58, 189.5)	78.5 (53.8, 153.5)	100 (63, 207)	.89	1.16 (0.67, 2.01)
Color Trails #2	151.5 (106, 241)	137 (100, 241)	179 (111.75, 241)	.82	1.22 (0.70, 2.11)
COWAT	20 (10, 28)	21 (11, 27.5)	20 (9, 29)	.24	0.80 (0.46, 1.38)
Category Fluency - Animals	12 (7, 16)	12 (7, 17)	12 (6, 15)	.71	0.93 (0.54, 1.61)
Category Fluency - Actions	7 (3, 10)	7 (3.5, 10)	7 (3, 10)	.34	0.84 (0.49, 1.46)
PASAT	17 (6, 25)	17.5 (8.75, 25)	17 (5, 24)	.96	1.12 (0.64, 1.96)
Sensitivity analyses--Composite					
Actual Treatment Received	73 (58, 80)	73 (57, 80)	74 (58, 80)	.21	0.89 (0.55, 1.43)

1 Cells report the Median (25th %ile, 75th %ile) unless otherwise noted. All neuropsychological scores are raw performance scores rather than scaled scores. "UNT" means untestable due to severity of CNS impairment

2 Statistical significance by blocked Wilcoxon[21,24] stratifying on site and age/severity from the randomization

3 Proportional odds ratio reported with 95% confidence interval, adjusting for site and age/severity from the randomization. A value >1 indicates a better disposition for the ICP group

4 Statistical significance by Fisher's exact test

Table S8 - Subgroup Analyses on the primary composite outcome and on GOS-E All but the analyses based on sex are post hoc.

Composite Outcome		**N**	**Overall**	**ICP**	**Imaging / Clinical Exam**	**P Value** [1]	**Proportional Odds Ratio** [2]
Sex	Male	283	52	53	51	.65	1.09 (0.73, 1.64)
	Female	41	48	48	48	.91	1.34 (0.38, 4.75)
Site	Japones	76	58	61	56	.56	1.28 (0.59, 2.80)
	San Juan de Dios	88	54	55	53	.53	1.15 (0.56, 2.39)
	Viedma	69	54	54	53	.66	1.08 (0.48, 2.44)
	Vernaza	19	50	58	44	.84	1.81 (0.36, 9.24)
	Tarija	52	40	38	43	.63	0.70 (0.27, 1.80)
	Espejo	20	38	43	34	.97	1.50 (0.32, 6.97)
Marshall [3]	I,II	45	59	60	58	.99	0.70 (0.22, 2.20)
	III	138	53	54	52	.23	1.32 (0.72, 2.41)
	IV	22	40	53	29	.16	5.57 (0.87, 35.63)
	Mass Lesion [4]	117	48	47	50	.55	1.05 (0.55, 2.01)
Age	13-24	123	58	62	54	.42	1.63 (0.87, 3.04)
	25-39	97	55	54	56	.86	0.78 (0.38, 1.61)
	40+	104	40	40	40	.99	1.11 (0.56, 2.17)
6-Month GOS-E		**N**	**Overall**	**ICP**	**Imaging / Clinical Exam**	**P Value** [1]	**Proportional Odds Ratio** [2]
Sex	Male	258	3.9	4.1	3.8	.52	1.14 (0.72, 1.80)
	Female	37	3.3	3.4	3.2	.55	4.21 (0.81, 21.80)
Site	Japones	67	4.8	5.0	4.5	.41	1.51 (0.62, 3.66)

	San Juan de Dios	82	3.9	4.1	3.7	.49	1.35 (0.58, 3.13)
	Viedma	64	4.4	4.5	4.3	.75	1.13 (0.45, 2.83)
	Vernaza	18	3.3	4.1	2.8	.42	3.07 (0.48, 19.71)
	Tarija	49	2.6	2.4	2.8	.47	0.66 (0.21, 2.04)
	Espejo	16	2.1	2.4	1.9	.48	2.23 (0.27, 18.53)
Marshall [3]	I,II	38	4.4	5.1	3.7	.36	2.04 (0.54, 7.67)
	III	127	4.1	4.2	3.9	.18	1.46 (0.75, 2.87)
	IV	22	3.0	4.5	1.8	.35	4.37 (0.45, 42.72)
	Mass Lesion [4]	107	3.5	3.2	3.8	.71	0.74 (0.35, 1.56)
Age	13-24	112	4.7	5.2	4.3	.09	2.10 (1.03, 4.27)
	25-39	87	4.2	4.3	4.2	.78	1.16 (0.50, 2.70)
	40+	96	2.5	2.4	2.6	.83	0.91 (0.40, 2.05)

1 Statistical significance by blocked Wilcoxon stratifying on site and age/severity from the randomization. Cells contain mean Composite and mean GOS-E score

2 Proportional odds ratio reported with 95% confidence interval. A value >1 indicates a better disposition for the ICP group

3 Marshall grade from initial CT scan

4 Both evacuated and non-evacuated

Table S9a - Processes of Care, all randomized cases

	All Subjects				
	Total	**ICP**	**Imaging / Clinical Exam**	**P Value [1]**	**Proportional Odds Ratio or P Value [2]**
N	324	157	167		
ICP-related variables					
Duration of ICP Monitoring					
Mean ± SD	4.5 ± 3.5	4.5 ± 3.5			
Median (IQR)	3.5 (1.9, 6.6)	3.5 (1.9, 6.6)	---	---	---
0-23 hrs	16 (10%)	16 (10%)	---	---	---
1-2 days	53 (34%)	53 (34%)	---		
3-5 days	41 (26%)	41 (26%)	---		
6-7 days	21 (13%)	21 (13%)	---		
8+ days	25 (16%)	25 (16%)	---		
Unknown	1	1			
First ICP≥20 n(%)	55 (37%)	55 (37%)			
ICP≥20 at any point n(%)	116 (79%)	116 (79%)			
Number of Hourly ICP≥20					
Mean ± SD	24.7 ± 39.9	24.7 ± 39.9			
Median (IQR)	6 (1, 33)	6 (1, 33)			
% of Hourly ICP≥20					

	All Subjects				
	Total	**ICP**	**Imaging / Clinical Exam**	**P Value [1]**	**Proportional Odds Ratio or P Value [2]**
Mean ± SD	20 ± 28	20 ± 28			
Median (IQR)	7 (1, 31)	7 (1, 31)			
First CPP≤60	55 (37%)	55 (37%)			
CPP≤60 at any point	127 (86%)	127 (86%)			
Number of Hourly CPP≤60					
Mean ± SD	15.8 ± 21.4	15.8 ± 21.4			
Median (IQR)	6 (1, 24)	6 (1, 24)			
% of Hourly CPP≤60					
Mean ± SD	19% ± 29%	19% ± 29%			
Median (IQR)	6 (2, 21)	6 (2, 21)			
<u>Protocol-specified Comparisons</u>					
ICU Length of Stay					
Median (IQR)	10 (6, 16)	12 (6, 17)	9 (6, 16)	.25	0.81 (0.55, 1.18)
0-3 days	42 (13%)	22 (14%)	20 (12%)	.41	
4-7 days	78 (25%)	30 (20%)	48 (29%)		
8-14 days	87 (27%)	42 (28%)	45 (27%)		
15-28 days	98 (31%)	51 (34%)	47 (28%)		
29+ days	13 (4%)	7 (5%)	6 (4%)		

	All Subjects				
	Total	**ICP**	**Imaging / Clinical Exam**	**P Value [1]**	**Proportional Odds Ratio or P Value [2]**
Unknown	6	5	1		
ICU Length of Stay with Brain-Specific Treatment (days) [3]					
Median (IQR)	4.0 (1.6, 7.2)	3.4 (1.1, 7.0)	4.8 (2.3, 7.4)	**.002**	1.87 (1.28, 2.75)
Respiratory Complications	201 (62%)	93 (59%)	108 (65%)	.36	1.00 (0.63, 1.59)
Sepsis	28 (9%)	16 (10%)	12 (7%)	.43	0.61 (0.27, 1.41)
Decubitus Ulcers	27 (8%)	19 (12%)	8 (5%)	**.03**	0.35 (0.15, 0.85)
Non-Neurological Complications	281 (87%)	134 (85%)	147 (88%)	.52	1.20 (0.62, 2.34)
<u>Post-hoc Comparisons</u>					
Acute-Care Length of Stay					
Median (IQR)	22 (8, 37)	24 (12, 39)	20 (7, 32)	**.04**	0.70 (0.48, 1.03)
0-3 days	37 (11%)	20 (13%)	17 (10%)	.11	
4-7 days	39 (12%)	14 (9%)	25 (15%)		
8-14 days	40 (12%)	14 (9%)	26 (16%)		
15-28 days	89 (28%)	43 (28%)	46 (28%)		

	All Subjects				
	Total	**ICP**	**Imaging / Clinical Exam**	**P Value [1]**	**Proportional Odds Ratio or P Value [2]**
5-7 weeks	76 (24%)	40 (26%)	36 (22%)		
8+ weeks	41 (13%)	25 (16%)	16 (10%)		
Unknown	2	1	1		
Ventilator Days					
Median (IQR)	7 (4, 11)	7 (4, 11)	7 (4, 11)	.95	1.03 (0.70, 1.50)
Neuroworsening After Randomization					
No	243 (75%)	121 (78%)	122 (73%)	.44	1.29 (0.74, 2.25)
Yes	79 (25%)	35 (22%)	44 (27%)		
Unknown	2	1	1		
Integrated Brain-Specific Treatment Intensity [4]					
Median (IQR)	98 (29, 210)	69 (13, 181)	125 (45, 233)	**<.001**	2.36 (1.60, 3.47)
Treatments for Intracranial Hypertension					
Mechanical Ventilation[5]	100% (126.3)	100% (123.9)	100% (128.5)	---[6]	.42[7]
Sedation[5]	99% (107.0)	99% (108.3)	99% (105.7)	1.00[6]	.83[7]
Analgesia[5]	99% (111.9)	99% (114.1)	99% (109.8)	1.00[6]	.78[7]

	All Subjects				
	Total	**ICP**	**Imaging / Clinical Exam**	**P Value [1]**	**Proportional Odds Ratio or P Value [2]**
Paralytics[5]	8% (10.9)	11% (14.2)	5% (3.9)	.06[6]	.51[7]
Mannitol (any dose)[5]	54% (17.0)	51% (**12.6**)	57% (**20.8**)	.37[6]	**<.001**[7]
Mannitol (high dose)[5]	5% (3.7)	4% (4.3)	5% (3.3)	1.00[6]	.87[7]
Hypertonic Saline (any dose)[5]	65% (16.4)	**58% (9.9)**	**72% (21.3)**	**.01**[6]	**<.001**[7]
Hypertonic Saline (high dose)[5]	6% (2.3)	**10%** (2.5)	**3%** (1.6)	**.02**[6]	.40[7]
CSF drain[5]	1% (87.5)	1% (346.0)	2% (1.3)	.62[6]	.50[7]
Furosemide[5]	6% (17.3)	4% (23.2)	8% (14.5)	.16[6]	.64[7]
Pressors[5]	62% (97.5)	62% (100.0)	62% (95.1)	1.00[6]	.61[7]
High dose barbiturates[5]	19% (84.7)	**24%** (81.4)	**13%** (90.5)	**.02**[6]	.80[7]
Hyperventilation (any dose)[5]	67% (64.5)	**60% (38.9)**	**73% (84.0)**	**.009**[6]	**<.001**[7]
Hyperventilation to P_aCO_2 < 30 mm Hg[5]	18% (16.2)	21% (21.1)	16% (10.4)	.39[6]	.09[7]
Barbiturates	60 (19%)	38 (24%)	22 (13%)	**.02**	0.46 (0.25, 0.83)
Neurosurgical Procedures					
None	172 (53%)	87 (56%)	85 (51%)	.44	0.83 (0.54, 1.30)
Epidural/Subdural	112 (35%)	51 (33%)	61 (37%)	.48	1.19 (0.75, 1.89)
Contusions/Intracerebral	36 (11%)	15 (10%)	21 (13%)	.48	1.40 (0.68, 2.88)
Craniectomy	93 (29%)	44 (28%)	49 (30%)	.81	1.04 (0.63, 1.69)
Craniectomy alone	18 (6%)	9 (6%)	9 (5%)	1.00	0.93 (0.35, 2.42)

	All Subjects				
	Total	**ICP**	**Imaging / Clinical Exam**	**P Value [1]**	**Proportional Odds Ratio or P Value [2]**
Craniectomy with other NS	75 (23%)	35 (22%)	40 (24%)	.79	1.07 (0.63, 1.80)
Any neurosurgery	150 (47%)	69 (44%)	81 (49%)	.44	1.20 (0.77, 1.87)
Unknown	2	1	1		

1 All tests of significance exclude the N/A and unknown categories. P-values on rows with a median and interquartile range are from Blocked Wilcoxon[21,24] tests while those on the row for the first category are from Fisher exact tests. For treatments for intracranial hypertension, this column contains the P value based on Fisher exact tests comparing the number of participants who got that therapy.

2 Proportional odds ratio reported with 95% confidence interval is shwn in this column for most measures. A value >1 indicates a better disposition for the ICP group. For treatments for intracranial hypertension, this column contains the P value based on a Mann-Whitney test comparing the number of hours for those who received the treatment

3 Defined as the time between the first and last use of a brain-specific treatment (i.e. excluding ventilation, sedation, or analgesia)

4 Number of different intracranial hypertension treatments per hour, summed over the duration, and counting high-dose as double

5 Cells report the proportion of subjects who had each intracranial hypertension treatment, and the average number of hours per subject (among those who had the treatment). Values in bold are statistically significant.

6 P-value for comparing percent receiving the treatment (Fisher's exact test)

7 P-value for comparing number of hours for those who received the treatment (Mann-Whitney U test)

Table S9b - Processes of Care, Brain-Specific Treatment Survivors

	Subjects who survived at least 1 complete day after last brain-specific therapy				
	Total	**ICP**	**Imaging / Clinical Exam**	**P Value [1]**	**Proportional Odds Ratio [2]**
N	260	130	130		
ICP-related variables					
Duration of ICP Monitoring					
Mean ± SD	5.0 ± 3.5	5.0 ± 3.5			
Median (IQR)	4.0 (2.4, 7.0)	4.0 (2.4, 7.0)	---	---	---
0-23 hrs	4 (3%)	4 (3%)	---	---	---
1-2 days	45 (35%)	45 (35%)	---		
3-5 days	38 (29%)	38 (29%)	---		
6-7 days	17 (13%)	17 (13%)	---		
8+ days	25 (19%)	25 (19%)	---		
Unknown	1	1			
First ICP≥20 n(%)	36 (29%)	36 (29%)			
ICP≥20 at any point n(%)	95 (76%)	95 (76%)			
Number of Hourly ICP≥20					
Mean ± SD	23.4 ± 41.9	23.4 ± 41.9			
Median (IQR)	5 (1, 25.5)	5 (1, 25.5)			

	Subjects who survived at least 1 complete day after last brain-specific therapy				
	Total	**ICP**	**Imaging / Clinical Exam**	**P Value [1]**	**Proportional Odds Ratio [2]**
% of Hourly ICP≥20					
Mean ± SD	13 ± 19	13 ± 19			
Median (IQR)	5 (1, 17)	5 (1, 17)			
First CPP≤60	38 (30%)	38 (30%)			
CPP≤60 at any point	106 (85%)	106 (85%)			
Number of Hourly CPP≤60					
Mean ± SD	13.0 ± 19.8	13.0 ± 19.8			
Median (IQR)	5 (1, 16)	5 (1, 16)			
% of Hourly CPP≤60					
Mean ± SD	11% ± 16%	11% ± 16%			
Median (IQR)	4 (1, 15)	4 (1, 15)			
Protocol-specified Comparisons					
ICU Length of Stay					
Median (IQR)	13 (8, 18)	14 (8, 18)	12 (7, 17)	.32	0.82 (0.53, 1.26)
0-3 days	7 (3%)	4 (3%)	3 (2%)	.63	
4-7 days	55 (22%)	22 (18%)	33 (26%)		
8-14 days	81 (32%)	41 (33%)	40 (31%)		
15-28 days	98 (39%)	51 (41%)	47 (36%)		

	Subjects who survived at least 1 complete day after last brain-specific therapy				
	Total	**ICP**	**Imaging / Clinical Exam**	**P Value [1]**	**Proportional Odds Ratio [2]**
29+ days	13 (5%)	7 (6%)	6 (5%)		
Unknown	6	5	1		
	64	27	37		
ICU Length of Stay with Brain-Specific Treatment (days) [3]					
Median (IQR)	4.2 (2.0, 7.9)	3.8 (1.2, 7.6)	5.4 (2.6, 7.9)	**<.001**	2.16 (1.40, 3.32)
Respiratory Complications	147 (57%)	72 (55%)	75 (58%)	.80	1.11 (0.67, 1.86)
Sepsis	26 (10%)	15 (12%)	11 (9%)	.54	0.59 (0.24, 1.48)
Decubitus Ulcers	25 (10%)	19 (15%)	6 (5%)	**.01**	0.26 (0.10, 0.69)
Non-Neurological Complications	220 (85%)	108 (83%)	112 (86%)	.61	1.41 (0.66, 3.03)
Post-hoc Comparisons					
Acute-Care Length of Stay					
Median (IQR)	26 (17, 41)	29 (19, 42)	25 (15, 39)	.08	0.68 (0.45, 1.05)
0-3 days	2 (1%)	2 (2%)	0 (0%)	.22	
4-7 days	16 (6%)	6 (5%)	10 (8%)		
8-14 days	34 (13%)	13 (10%)	21 (16%)		

	Subjects who survived at least 1 complete day after last brain-specific therapy				
	Total	**ICP**	**Imaging / Clinical Exam**	**P Value [1]**	**Proportional Odds Ratio [2]**
15-28 days	89 (34%)	43 (33%)	46 (36%)		
5-7 weeks	76 (29%)	40 (31%)	36 (28%)		
8+ weeks	41 (16%)	25 (19%)	16 (12%)		
Unknown	2	1	1		
Ventilator Days					
Median (IQR)	8 (5, 12)	8 (5, 13)	8 (5, 13)	.90	1.07 (0.70, 1.64)
Neuroworsening After Randomization					
No	218 (85%)	109 (85%)	109 (85%)	1.00	1.06 (0.52, 2.18)
Yes	40 (16%)	20 (16%)	20 (16%)		
Unknown	2	1	1		
Integrated Brain-Specific Treatment Intensity [4]					
Median (IQR)	101 (27, 209)	55 (7, 192)	134 (59, 224)	**<.001**	2.75 (1.78, 4.27)
Barbiturates	39 (15%)	27 (21%)	12 (9%)	**.01**	0.36 (0.17, 0.77)
Neurosurgical Procedures					
None	138 (54%)	70 (54%)	68 (53%)	.90	0.93 (0.57, 1.54)

	Subjects who survived at least 1 complete day after last brain-specific therapy				
	Total	**ICP**	**Imaging / Clinical Exam**	**P Value [1]**	**Proportional Odds Ratio [2]**
Epidural/Subdural	93 (36%)	43 (33%)	50 (39%)	.44	1.26 (0.75, 2.11)
Contusions/Intracerebral	30 (12%)	13 (10%)	17 (13%)	.56	1.43 (0.65, 3.14)
Craniectomy	67 (26%)	35 (27%)	32 (25%)	.78	0.89 (0.50, 1.56)
Craniectomy alone	12 (5%)	9 (7%)	3 (2%)	.14	0.32 (0.08, 1.22)
Craniectomy with other NS	55 (21%)	26 (20%)	29 (22%)	.76	1.16 (0.63, 2.11)
Any neurosurgery	120 (47%)	59 (46%)	61 (47%)	.90	1.07 (0.65, 1.77)
Unknown	2	1	1		

1 All tests of significance exclude the N/A and unknown categories. P-values on rows with a median and interquartile range are from Blocked Wilcoxon[21,24] tests while those on the row for the first category are from Fisher exact tests.

2 Proportional odds ratio reported with 95% confidence interval. A value >1 indicates a better disposition for the ICP group

3 Defined as the time between the first and last use of a brain-specific treatment (i.e. excluding ventilation, sedation, or analgesia)

4 Number of different intracranial hypertension treatments per hour, summed over the duration, and counting high-dose as double

Table S10a - Catheter-related or Serious Adverse Events Individual terms are shown for probably related events or events occurring in 5 or more people

	Total	ICP	Imaging / Clinical Exam	P Value [1]
N	324	157	167	
Catheter-related (None met criteria for Serious Adverse Event)	10 (3%)	10 (6%)	---	---
ICP catheter related infection	0 (0%)	0 (0%)	---	---
ICP catheter malfunction	4 (1%)	4 (3%)	---	---
Unplanned ICP catheter removal	4 (1%)	4 (3%)	---	---
ICP catheter related hemorrhage	2 (1%)	2 (1%)	---	---
Any SAE	146 (45%)	70 (45%)	76 (46%)	.91
Infections	23 (7%)	13 (8%)	10 (6%)	.52
Pneumonia	9 (3%)	5 (3%)	4 (2%)	.74
Sepsis	6 (2%)	2 (1%)	4 (2%)	.69
Nervous system	5 (2%)	3 (2%)	2 (1%)	.68
Nervous System excluding infections	48 (15%)	19 (12%)	29 (17%)	.21
Intracranial hypertension	37 (11%)	14 (9%)	23 (14%)	.22
Respiratory System excluding infections	17 (5%)	9 (6%)	8 (5%)	.81
ARDS	6 (2%)	3 (2%)	3 (2%)	1.00

	Total	ICP	Imaging / Clinical Exam	P Value [1]
Respiratory failure	9 (3%)	4 (3%)	5 (3%)	1.00
Cardiovascular System	30 (9%)	17 (11%)	13 (8%)	.44
Shock	10 (3%)	5 (3%)	5 (3%)	1.00
Cardiac arrest	18 (6%)	11 (7%)	7 (4%)	.33
Urinary System	3 (1%)	1 (1%)	2 (1%)	1.00
Gastrointestinal System	2 (1%)	0 (0%)	2 (1%)	.50
Metabolism	3 (1%)	2 (1%)	1 (1%)	.61
Skin and Skeletal Muscle	2 (1%)	2 (1%)	0 (0%)	.23
Death (unspecified cause)	24 (7%)	12 (8%)	12 (7%)	1.00
Hematological	0 (0%)	0 (0%)	0 (0%)	---
Other	4 (1%)	2 (1%)	2 (1%)	1.00

1 P value by Fisher exact test

Table S10b - Adverse Events Complications are shown by category. Individual terms are shown for events occurring in at least 10% of cases on a single treatment.

	Total	**ICP**	**Imaging / Clinical Exam**	**P Value** [1]
N	322	156	166	
Unknown	2	1	1	
Infections	160 (50%)	76 (49%)	84 (51%)	.74
Pneumonia	130 (40%)	62 (40%)	68 (41%)	.91
Sepsis	27 (8%)	16 (10%)	11 (7%)	.31
Nervous System	16 (5%)	8 (5%)	8 (5%)	1.00
Respiratory System	32 (10%)	15 (10%)	17 (10%)	1.00
Cardiovascular System	18 (6%)	9 (6%)	9 (5%)	1.00
Urinary System	11 (3%)	5 (3%)	6 (4%)	1.00
Gastrointestinal System	1 (0%)	1 (1%)	0 (0%)	.48
Metabolism	194 (60%)	93 (60%)	101 (61%)	.91
Hyponatremia	110 (34%)	52 (33%)	58 (35%)	.81
Hypernatremia	87 (27%)	40 (26%)	47 (28%)	.62
Other	124 (39%)	63 (40%)	61 (37%)	.57
Skin and Skeletal Muscle	27 (8%)	19 (12%)	8 (5%)	**.03**
Decubitus Ulcers	27 (8%)	19 (12%)	8 (5%)	**.03**
Unspecified death	75 (23%)	32 (21%)	43 (26%)	.29
Hematological	34 (11%)	13 (8%)	21 (13%)	.28
Coagulopathy	34 (11%)	13 (8%)	21 (13%)	.28

	Total	ICP	Imaging / Clinical Exam	P Value [1]
Other	184 (57%)	84 (54%)	100 (60%)	.26

1 Statistical significance by Fisher exact test

Acronyms

1.	**Abbreviated injury scale**	**AIS**
2.	**Acute Respiratory Distress Syndrome**	**ARDS**
3.	**Brain-specific treatment**	**BST**
4.	**Brain trauma**	**BT**
5.	**Brain Trauma Foundation**	**BTF**
6.	**Cat scan**	**CT**
7.	**Cerebral perfusion pressure**	**CPP**
8.	**Controlled Oral Word Association Test**	**COWAT**
9.	**Data Safety Monitoring Board**	**DSMB**
10.	**Disability Rating Scale**	**DRS**
11.	**Federal wide assurance**	**FWA**
12.	**Glasgow coma scale**	**GCS**
13.	**Galveston Orientation and Amnesia Test**	**GOAT**
14.	**High income countries**	**HICs**
15.	**Imaging and clinical examination**	**ICE**
16.	**Intensive care unit**	**ICU**
17.	**Internal review board**	**IRB**
18.	**Interquartile range**	**IQR**
19.	**Intracranial hypertension**	**ICHy**
20.	**Intracranial pressure monitor**	**ICP**
21.	**Length of stay**	**LOS**

22.	**Lower-middle income countries**	**LMICs**
23.	**Mini-Mental State Exam**	**MMSE**
24.	**National Institute of Health**	**NIH**
25.	**National Institute Neurological Disorders and Stroke**	**NINDS**
26.	**Randomized control trial**	**RCT**
27.	**Severe traumatic brain injury**	**sTBI**
28.	**Therapeutic intensity level**	**TIL**
29.	**Wechsler Adult Intelligence Scale**	**WAIS**

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