**Supplemental Data File**

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| **Supplemental Table 1: Inclusion/Exclusion Criteria** |
| Inclusion Criteria | Exclusion Criteria |
| Male and female patients | Neurological exam suggested imminent brain death |
| Age: 14 years and older | Accuracy of neurologic exam was uncertain (e.g., seizure activity) |
| Non-penetrating severe TBI(initial GCS score 3-8, motor score ≤5, not following commands after resuscitation and without influence of paralytics or sedation) | Potential secondary oxygenation concerns which would influence results (e.g., evidence of severe chest/lung injury), refractory hypotension; and/or systemic hypoxia  |
| Clinical need for ICP monitoring according to Guidelines for the Management of Severe TBI | Placement of an intracranial monitor was contraindicated |
| Randomization and ICP monitor placement within 12 hours of injury | Pregnancy |
| Inability to obtain informed consent from legal authorized representative (LAR) |
| Participation in another interventional trial |
| PbtO2 monitoring before randomization |

| **Supplemental Table 2: Interventions by assignment group** |
| --- |
|  | **ICP Only**(N=62) | **ICP + PbtO2**(N=57) |
| Total Number of Interventions | 933 | 867 |
|  B | 933 | 411 |
|  C | --- | 334 |
|  D | --- | 122 |
| Add antiepileptic drug (AED) | --- | 9 |
|  C | --- | 8 |
|  D | --- | 1 |
| Add EEG monitoring | --- | 10 |
|  C | --- | 10 |
|  D | --- | 0 |
| Adjust head of bed to improve brain oxygenation | --- | 39 |
|  C | --- | 39 |
| Adjust head of bed to lower ICP | 104 | 56 |
|  B | 104 | 46 |
|  D | --- | 10 |
| Adjust sedation and analgesia | 340 | 210 |
|  B | 340 | 184 |
|  D | --- | 26 |
| Adjust Temperature to 32 – 34.5°C | 1 | 0 |
|  B | 1 | 0 |
|  D | --- | 0 |
| Adjust temperature to 35 – 37°C | 4 | 6 |
|  B | 4 | 4 |
|  D | --- | 2 |
| Adjust ventilation to increase PaCO2 to 45‐50 mmHg | --- | 6 |
|  C | --- | 6 |
| Adjust ventilation to lower PaCO2 to 32‐35 mmHg. | 9 | 6 |
|  B | 9 | 6 |
| Adjust ventilation to obtain PaCO2 between 35‐40 mmHg | 39 | 10 |
|  B | 39 | 10 |
| CSF drainage | 169 | 68 |
|  B | 169 | 61 |
|  D | --- | 7 |
| Decompressive craniectomy | 3 | 0 |
|  B | 3 | 0 |
|  D | --- | 0 |
| Decrease ICP to < 10mmHg | --- | 11 |
|  C | --- | 11 |
| Ensure temperature < 38°C | 98 | 90 |
|  B | 98 | 33 |
|  C | --- | 42 |
|  D | --- | 15 |
| High dose mannitol (>1g/kg), or higher frequency of standard dose | 6 | 6 |
|  B | 6 | 6 |
|  D | --- | 0 |
| Hypertonic saline | 71 | 35 |
|  B | 71 | 28 |
|  D | --- | 7 |
| Increase CPP to a maximum of 70mmHg with fluid bolus | --- | 35 |
|  C | --- | 27 |
|  D | --- | 8 |
| Increase CPP to a maximum of 70mmHg with vasopressors | --- | 6 |
|  C | --- | 5 |
|  D | --- | 1 |
| Increase PaO2 by adjusting PEEP | --- | 57 |
|  C | --- | 48 |
|  D | --- | 9 |
| Increase PaO2 by increasing FiO2 to 100% | --- | 38 |
|  C | --- | 26 |
|  D | --- | 12 |
| Increase PaO2 by increasing FiO2 to 60% | --- | 102 |
|  C | --- | 83 |
|  D | --- | 19 |
| Neuromuscular paralysis | 8 | 3 |
|  B | 8 | 2 |
|  D | --- | 1 |
| Optimize hemodynamics | --- | 25 |
|  C | --- | 25 |
| Pentobarbital coma | 1 | 0 |
|  B | 1 | 0 |
|  D | --- | 0 |
| Repeat CT – look for increased size of intracranial mass lesions | 14 | 9 |
|  B | 14 | 7 |
|  D | --- | 2 |
| Standard dose mannitol (0.25 – 1.0 g/kg) | 66 | 24 |
|  B | 66 | 23 |
|  D | --- | 1 |
| Transfuse packed RBCs to reach Hgb > 10g/dL | --- | 5 |
|  C | --- | 4 |
|  D | --- | 1 |
| Treat surgically remediable lesions with craniotomy | --- | 1 |
|  B | --- | 1 |
|  D | --- | 0 |

**Supplemental Table 3: Treatment-related protocol deviations & violations in each study group.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***By Number of Patients*** | **Overall** | **ICP Only** | **PbtO2 + ICP** | ***p*-value** |
| **N** | **119** | **62** | **57** |  |
| Deviation: ICP 20-25 mmHg for >30 min. | 45 (38%) | 25 (40%) | 20 (35%) | .576 |
| Deviation: PbtO2 15-19 mmHg for >30 min. | 11 (9%) | --- | 11 (19%) | --- |
| Violation: ICP >25mmHg for >30 min. | 14 (12%) | 8 (13%) | 6 (11%) | .780 |
| Violation: PbtO2 <15mmHg for >30 min. | 9 (8%) | --- | 9 (16%) | --- |

**Supplemental Table 4: Serious Adverse Events.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Overall** | **ICP Only** | **PbtO2 + ICP** | ***p*-value** |
| **Subjects** | **119** | **62** | **57** |  |
| A - Cardio-Vascular  | 14 (12%) | 5 (8%) | 9 (16%) | .257 |
| B - Genito-Urinary  | 0 (0%) | 0 (0%) | 0 (0%) | --- |
| C - Gastro-intestinal  | 2 (2%) | 1 (2%) | 1 (2%) | 1.000 |
| D - Laboratory abnormalities  | 0 (0%) | 0 (0%) | 0 (0%) | --- |
| E - Metabolic Disorders  | 0 (0%) | 0 (0%) | 0 (0%) | --- |
| F - Musculo-skeletal  | 0 (0%) | 0 (0%) | 0 (0%) | --- |
| G - Neurological  | 15 (13%) | 10 (16%) | 5 (9%) | .276 |
| H - Opthamologic  | 0 (0%) | 0 (0%) | 0 (0%) | --- |
| I - Respiratory  | 5 (4%) | 1 (2%) | 4 (7%) | .192 |
| J - Skin | 0 (0%) | 0 (0%) | 0 (0%) | --- |
| K - Other  | 25 (21%) | 17 (27%) | 8 (14%) | .114 |
|  Death following w/d of medical care | 22 (18%) | 14 (23%) | 8 (14%) | .248 |
|  Other\* | 3 (3%) | 3 (5%) | 0 (0%) | .245 |

\* *"sepsis", "MRSA infection", "self-extubation"*

**Web Appendix – BOOST-II tiered interventions for each treatment scenario.**



For Type B treatments (ICP ≥ 20 mm Hg), Tier 1 treatment interventions included adjustment of the head of the bed; ensuring body temperature < 38oC; titration of pharmacologic analgesia and sedation; drainage of CSF if ventriculostomy present; and/or administration of mannitol or hypertonic saline. Tier 2 treatment interventions were initiated when ICP was ≥ 20 mm Hg for >60 minutes despite Tier 1 therapies and included adjustment of ventilator rate (paCO2 32-35 mmHg); increased dosage of osmotics; repeat CT scan to determine if intracranial mass lesions increased in volume, with surgery if applicable; optimization of hemodynamics and adjustment of body temperature (35-37oC). Tier 3 therapies were optional, instituted per attending site physician discretion and included pentobarbital coma, according to local protocol; decompressive craniectomy; hypothermia treatment (32-34.5oC); and neuromuscular paralysis.

 For Type C treatments (ICP normal, pBtO2 <20 mm Hg), Tier 1 treatment interventions included adjustment of the head of the bed; ensuring body temperature < 38oC; optimization of hemodynamics with increase cerebral perfusion pressure (CPP) > 70mmHg; optimization of oxygenation (increasing PaO2 with FiO2 at 60% and increasing PEEP); considering EEG monitoring and potential additional seizure prophylaxis. Tier 2 treatment interventions were initiated when PbtO2 was < 20mm Hg for >60 minutes despite Tier 1 therapies and included additional adjustments of ventilator parameters (increasing PaO2 with FiO2 at 100% and increasing PEEP; increasing PaCO2 45-50mm Hg; ); optimization of hemodynamics to increase CPP to 7-mmHg (with vasopressors, if needed and decrease ICP to <10mmHg by CSF drainage and/or increased sedation) and transfusion of pRBC’s to Hgb >10mmHg.

 For Type D treatments (ICP ≥ 20 and PbtO2 < 20 mm Hg), Tier 1 treatment interventions included adjustment of the head of the bed; ensuring body temperature < 38oC; titration of pharmacologic analgesia and sedation; drainage of CSF if ventriculostomy present; and/or administration of mannitol or hypertonic saline; optimization of hemodynamics to maximum of 70mmHg with fluid bolus; optimization of oxygenation (increasing PaO2 with FiO2 at 60% and increasing PEEP); and consideration of EEG monitoring and potential additional seizure prophylaxis. Tier 2 treatment interventions then included adjustment of ventilator rate (increasing PaO2 with FiO2 at 100% and increasing PEEP); increased dosage of osmotics; repeat CT scan to determine if intracranial mass lesions increased in volume, with surgery if applicable; optimization of hemodynamics (increase CPP to >70 mmHg and transfusion of pRBC’s to Hgb >10mmHg); adjustment of body temperature (35-37oC). Tier 3 therapies were optional, instituted per attending site physician discretion and included pentobarbital coma, according to local protocol; decompressive craniectomy; hypothermia treatment (32-34.5oC); and neuromuscular paralysis.