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TITLE:

A Bedside, Single Burr Hole Approach to Multimodality Monitoring in Severe Brain Injury

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KEYWORDS:

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SUMMARY:

A method of recording multimodality monitoring signals in patients with severe brain injuries using a bedside, single burr hole technique is described.

ABSTRACT:

Intracranial pressure (ICP) monitoring is a cornerstone of the intensive care management of patients with severe acute brain injuries, including traumatic brain injury. While elevations in ICP are common, data regarding the measurement and treatment of these ICP elevations are conflicting. There is increasing recognition that changes in the balance between supply and demand of brain tissue are critically important and therefore the measurement of multiple modalities is required. Approaches are not standard, and therefore this article provides a description of a bedside, single burr hole approach to multimodality monitoring that allows the passage of probes designed to measure not only ICP but brain tissue oxygen, blood flow, and intracranial electroencephalography. Patient selection criteria, operative procedures, and practical considerations for securing probes during critical care are described. This method is readily performed, safe, secure, and flexible for the adoption of a variety of multimodality monitoring approaches aimed at detecting or preventing secondary brain injuries.

INTRODUCTION:

Severe brain injuries such as traumatic brain injury (TBI) or subarachnoid hemorrhage may result in coma, a clinical state in which patients do not respond to their environment. Neurosurgeons and neurointensivists rely heavily on the clinical neurological exam, but severe brain injuries may make it impossible to detect changes related to the brain's physiologic environment: elevations in intracranial pressure (ICP), decreases in cerebral blood flow, or nonconvulsive seizures and spreading depolarizations. These physiologic disturbances can lead to further injury, termed secondary brain injury.

After severe traumatic brain injury, elevations in ICP are common and may result in decreased blood flow and therefore secondary brain injury and neurodeterioration. Elevations in ICP have been documented in up to 89% of patients¹ and neurodeterioration occurs in one-quarter, increasing mortality from 9.6% to 56.4%². Therefore, the measurement of ICP is the most commonly used biomarker for the development of secondary brain injury and has a Level IIb recommendation from the Brain Trauma Foundation³.

The measurement of ICP was pioneered over 50 years ago⁴ using catheters that were introduced through a twist drill craniostomy (often referred to interchangeably as a burr hole) typically created in the frontal bone at the mid-pupillary line just anterior to the coronal suture and passed into the ventricles. However, these external ventricular drainage catheters (EVDs) require midline anatomy, which is not always present after severe brain injuries, and misplacement can potentially damage deep structures such as the thalamus. Although EVDs allow drainage of CSF as a potential treatment option, the hemorrhage rates from EVDs are 6 - 7% on average^{5,6}.

Intraparenchymal pressure monitors are introduced *via* burr hole and are common alternatives and adjuncts to EVDs with hemorrhage rates of 3 - 5%^{7,8}. These are smaller probes that sit 2 - 3 cm under the inner table of the skull, and allow for continuous measurement of pressure but without an option to drain cerebrospinal fluid, as do EVDs. Existing cohort studies⁹ and meta-analyses^{10,11} suggest that targeting ICP as a marker of secondary brain injury may improve survival; however, a randomized controlled trial comparing treatment of ICP based on neurological exam alone vs. measured ICP failed to demonstrate benefit¹².

Advances in neurosurgery and neurointensive care have led to an understanding that brain physiology is more complicated than ICP alone. It has been demonstrated that autoregulatory function within the brain is impaired after brain injury¹³, leading to changes in the regulation of regional cerebral blood flow (rCBF). Further, the burden of nonconvulsive seizures¹⁴ and spreading depolarizations¹⁵ are being recognized using recordings from intracranial electroencephalography (iEEG) electrodes. Strategies to improve brain tissue oxygen (PbtO₂) were shown to be a target for therapy and proved feasible in a large, multicenter Phase II clinical trial¹⁶.

This article describes a technique that allows for the simultaneous measurement of multiple modalities – including ICP, PbtO₂, rCBF, and iEEG – using a simple, single burr hole placed at the bedside in patients with severe acute brain injuries requiring intensive care. Patient selection and surgical approach to this technique are included. This technique specifically allows for the

placement of multiple probes to provide targeted monitoring of multiple physiologic parameters that may provide a more sensitive and specific early warning system for secondary brain injuries.

PROTOCOL:

This protocol was developed as a standard of care. The retrospective use of data gathered during the course of care was approved through a waiver of informed consent by the University of Cincinnati's Institutional Review Board.

1. Patient Selection

1.1 Identify patient with acute brain injury (traumatic brain injury, stroke).

NOTE: Collaborative discussion between surgical and intensive care teams is critical to ensure that there is consensus on which acute brain injury processes warrant monitoring.

1.1.1 Rule out confounders that may cloud clinical examination including elevated alcohol level or toxic exposures.

1.1.2 Rule out contraindications to neurosurgical procedures, including but not limited to platelets < 100 g/dL, international normalized ratio > 1.5, recent administration of non-vitamin K antagonist anticoagulants; caution is warranted in those on dual antiplatelets (*e.g.*, both aspirin and clopidogrel).

1.2 Perform Glasgow Coma Scale score. Patients are excluded if they exhibit command following or if they cannot follow commands due to aphasia and have eye opening spontaneously or to voice.

1.3 Once a patient is considered eligible for advanced neuromonitoring, obtain operative consent after discussion of risks and benefits of the procedure.

NOTE: Risks include an overall risk of significant hemorrhage 1.9% and a theoretical risk of infection. Benefits include ability to monitor intracranial parameters for targeted therapies, although there is no class I evidence for the use of any intracranial monitoring modality.

2. Preparation of Site and Skin

2.1 Identify the correct location for placement of the bolt. This will be 11 cm from the nasion or 1 cm anterior to the coronal suture and 2 - 3 cm laterally at about the mid-pupillary line.

2.2 Clip hair in the region of the scalp through which the bolt will be placed as identified in step 2.1. Then re-identify the correct location once more and mark with a pen or a marker.

2.3 Immobilize the head by using tape or other securing strategy to ensure that the head does not move during the burr hole placement.

2.4 Sterilize the area using betadine solution, allowing the prepared area to dry fully.

NOTE: Commercial chlorhexidine solutions may contain indications that they are not for use when in contact with cerebrospinal fluid due to neurotoxicity.

2.5 Using 10 cc of 1% lidocaine with epinephrine, provide adequate analgesia to the location marked in step 2.2. Begin with the skin, creating a large wheal, then advance the needle to the periosteal surface and inject several cc as the needle is retracted slowly to the surface of the skin.

3. Preparation of Equipment

3.1 Set up a sterile table with the following equipment.

3.1.1 Prepare a cranial access kit or comparable set of instruments that include a scalpel blade, hemostat, forceps, gauze, and a hand-held twist drill.

3.1.2 Open intracranial monitors onto the sterile field (**Table 1** and **Table of Materials**), including (i) quad lumen bolt kit and locking nuts (up to 4); this kit will also include a 5.3 mm cranial drill bit to be used with the hand-held twist drill (step 3.1.1); (ii) the ICP/PbtO₂ probe; (iii) the rCBF probe; (iv) the depth electrode with stylet; (v) optionally (not shown), 70 microdialysis bolt catheter or other intracranial probe.

3.1.3 Thread each probe through a locking nut and subsequent insert through one of the lumens of the bolt. The ICP/PbtO₂ probe, the thickest probe, is placed preferentially in the tallest lumen, whereas the other probes can fit through any remaining lumens.

3.1.4 Measure the distance from the end of the bolt to the tip of each probe at 2.5 - 3 cm. Advance the depth electrode until the most proximal electrode is just outside the end of the bolt.

3.1.5 Once the probe is placed the appropriate distance from the end of the bolt, tighten the locking nut on the lumen of the bolt and then the probe itself, locking in place on the probe.

3.1.6 Once the locking nut is tight, loosen the nut from the lumen and remove each probe with its locking nut in place. Place on the sterile table next to the bolt.

4. Drilling a Burr Hole

4.1 Use scalpel to create a 1 - 2 cm incision in the anesthetized region (step 2.5). Use blunt tip instrument to separate subgaleal tissues, exposing periosteum.

4.2 Insert and use hex bit to tighten 5.3 mm drill bit to the cranial drill.

4.3 Place the cranial drill perpendicular to the skull. Use continuous pressure while rotating the drill. Continue to drill until there is a tactile change in pressure. Once it becomes harder to drill, the inner table of the skull has been reached. Continue drilling with counter upward support to avoid plunging the drill into the cortex.

4.4 Remove the drill and clear the burr hole of any bone chips or debris using a curet or hemostat.

4.5 Use a scalpel blade to incise the dura in a cruciate fashion. Confirm that the dura is completely open.

NOTE: Some practitioners may use alternative approaches, such as using an 18 G needle to perforate the dura using tactile feedback until the dura is sufficiently opened. Adequate durotomy is critical regardless of the technique, and incomplete durotomy may lead to difficulty passing thin, flexible catheters or malpositioning of the catheters.

5. Inserting the Cranial Bolt

5.1 Holding the bolt by the plastic wings, thread through the burr hole using a firm, clockwise twisting motion. Be careful not to overtighten, which can compress the adjacent skin and soft tissues.

NOTE: Cerebrospinal fluid may rise from the lumens of the bolt, particularly if there is increased intracranial pressure.

5.2 Insert each pre-measured probe until the locking nut meets the lumen.

5.2.1 The dura may provide resistance, particularly to thinner probes. Insert the thinnest probe first, which may help avoid pass resistance.

5.2.2 Insert the depth electrode with the stylet in place. Once placed and tightened on the lumen, gently loosen the locking nut from the probe just enough to remove the stylet, then re-tighten.

NOTE: Once all probes are locked onto the lumens through which they pass, the sterile part of the procedure is complete.

6. Securing the Probes

6.1 Have available personnel connect the ICP/PbtO₂ probe to the bedside monitor to assess the intracranial pressure and brain tissue oxygen.

6.2 Using silk or other durable tape, gently loop each probe and tape it to its lumen. This creates strain resistance. Use caution not to create a “kink” in the probes, as they have thin components that can break.

6.3 Optionally, use a large 6" x 2" tegaderm or a thin strip of occlusive petrolatum gauze to wrap the base of the bolt, reducing the exposure of the skin-to-burr-hole interface. The occlusive petrolatum gauze also provides bacteriostatic function.

6.4 Prior to transport, use a woven gauze to wrap the entire bolt, encompassing each of the unplugged probes within the roll, and tape the end with silk tape. This ensures that the loose ends of unplugged probes are not accidentally pulled during movement to and from operative or radiological beds.

7. Verifying Probe Data

7.1 Once an initial ICP is recorded, if it is clinically appropriate, order a noncontrast head computed tomography (CT) to verify the position of the bolt and the probes, which should sit within the frontal subcortical white matter. This will also expose any adverse events such as subdural or intraparenchymal hemorrhage that rarely occur during placement.

7.2 After verifying the position of the probes, plug all probes into local data recording system (equipment will vary). Perform some simple data verification steps that can be used for each modality to ensure the signal is recording as planned:

7.2.1 For intracranial pressure, verify that a pulsatile waveform is present. The ICP data measured by the ICP/PbtO₂ probe generates a waveform visible on the local recording system.

7.2.2 For brain tissue oxygen, first examine the temperature of the brain and verify that the temperature is similar to what would be expected for core body temperature measured at another site (bladder, esophageal). Second, verify the responsiveness of the monitor by transiently increasing the fraction of inspired oxygen (FiO₂) of the patient to 1.0 (100%).

NOTE: Within 15 min, the PbtO₂ should increase by at least 10 mmHg. If not, the diffusion of dissolved oxygen is being impeded either by a small hematoma (check CT scan from step 7.1) or local microtrauma induced by placement of the probe itself. Consider loosening the locking nut slightly and turning the probe clockwise 90° and re-tightening the locking nut in case there is a small amount of clotted blood accumulated on the oxygen entry surface of the probe.

7.2.3 For cerebral blood flow, first wait for the initial measurement, which may take up to 6 min for the probe to establish a stable thermal field.

7.2.3.1 Ensure that the blood flow probe temperature is within 0.7 °C of the brain tissue temperature.

NOTE: If lower, the blood flow probe is likely too shallow and will need to be advanced.

7.2.3.2 Ensure that the probe placement assistant (PPA) number, which is simultaneously generated with blood flow probe temperature in 7.2.3.1., reads < 2.

NOTE: This measurement is performed by a mechanical probe which senses displacement of the probe related to pulsatility, and values range from 0.0 (stable thermal field) to 10.0 (nearby pulsatile blood vessel render the thermal field too unstable to generate rCBF). If the PPA is > 2, consider pulling the probe back by 0.25 - 0.5 cm.

7.2.4 For depth electroencephalography (EEG), visually inspect the signal.

NOTE: The depth electrodes require a ground electrode and reference electrode. A local electrodiagnostic technologist will be able to assist in placing these electrodes. Correctly recorded EEG should demonstrate a mixture of frequencies at a 15 μ V/mm scale with a dynamic range \pm 200 - 400 μ V at a high-pass filter of 0.5 Hz and a low-pass filter of 50 Hz. If this is not seen, it may be worth verifying the placement of the reference or the ground.

8. Patient Care

NOTE: Following the procedure, no further pain control is necessary and no prophylactic antibiotics are required.

8.1 At the end of the clinical monitoring period, remove the bolt by first removing each of the probes individually. Then, twist the bolt counterclockwise until it comes loose from the skull and can be removed.

8.2 Use sterile technique to suture the skin opening and monitor for any cerebrospinal fluid leakage, bleeding, or swelling at the site.

REPRESENTATIVE RESULTS:

Experience in using this approach in 43 patients with severe TBI was recently published¹⁷. Patient selection limits the number of those eligible, but focusing on only those with TBI at a level I trauma center led to approximately 2 patients per month. This number is predicated on hospital volume and may increase if additional acute brain injuries are considered for monitoring, such as those with hemorrhagic stroke.

Placement may take place either in patients with non-surgical severe injuries or in those who have undergone surgery, depending on the preferences at an individual institution (**Figure 1**). This technique has been performed within a median of 12.5 h (interquartile range [IQR] 9.0 - 21.4 h) of injury and probes have been left *in situ* for a median of 97.1 h (IQR 46.9 - 124.6 h)¹⁷. Placement is typically within the non-dominant frontal lobe unless there is a contraindication. Three-quarters of bolts placed in dominant frontal lobe were placed contralateral to prior craniectomy. Nonetheless, in TBI, this strategy led to placement within an injured lobe the majority of the time. Misplacement was rare using this technique, occurring in only 6/42 (14.3%) of patients; device measurements were rarely affected¹⁷.

Bedside placement resulted in no adverse events at the time of bolt insertion. On follow up CT, small regions of peri-probe hematoma, pneumocephalus, or bone chips were found in 40.5% of patients¹⁷. However, mirroring the experience of other institutions¹⁸ that perform similar monitoring, only one expanding hematoma was considered to be a major hemorrhage. In this case, no surgical or medical intervention was recommended, and the patient outcome was felt not to be impacted. Across two cohorts including patients with TBI and subarachnoid hemorrhage, the overall rate of significant hemorrhage is 1.9%^{17,18}.

Once devices are in place, device dislodgement may occur and has been described as being related to the size of the probes, length of time they remain *in situ*, and relative complexity of moving, transferring, and caring for this patient population. More than half of patients experienced dislodgement of at least one probe before the end of their recording period, mostly commonly the rCBF probe. Limiting transportation may mitigate this risk: the number of trips that patients took appeared to be associated with devices becoming dislodged or no longer functioning (Wilcoxon rank sum test, $p = 0.03$)¹⁷. Nonetheless, this technique has resulted in measurements of all modalities in more than 90% of placements and most probes remain in place and generate continuous data for > 90% of the recording period.

FIGURE AND TABLE LEGENDS:

Figure 1: Clinical and radiologic placement of multimodality monitoring probes. (A) Appearance of bolt with three probes, as labelled prior to securing the probes or wrapping for transport. (B) Scout CT images (coronal and sagittal, respectively) demonstrating the trajectory of the probes approximately 1.5 cm (Depth) and 2-3 cm (ICP/PbtO₂, rCBF) below the inner table of the skull. (C) Axial CT after non-surgical severe TBI with excellent placement. Notice with standard windowing that the relatively dense probes may obscure subtle peri-probe hematoma. (D) Axial CT after surgical severe TBI demonstrating the placement of the bolt and probes contralateral to the hemicraniectomy site. (E) Incorrect (deep) placement of the probes after non-surgical severe TBI. Note that the probes are approaching the frontal horn of the lateral ventricle, indicating they are > 3 cm below the inner table of the skull. This placement may affect measurements obtained by the probes, although shallow, rather than deep, placement is more liable to create problems with rCBF and PbtO₂ measurements.

Table 1: Intracranial probes. The names of the probes used in this article and their measurements and sampling resolution. Please note that this is a representative list of probes that may be used for multimodality monitoring but does not represent an exhaustive list of the potential modalities that may be commercially available. EEG = electroencephalography; ICP = intracranial pressure; ICT = intracranial temperature; PbtO₂ = brain tissue oxygen; rCBF = regional cerebral blood flow.

DISCUSSION:

This article provides the practical elements of a method for introducing multiple probes into the brain follow acute brain injury in order to facilitate a multimodal approach to understanding the physiology underlying secondary brain injury. The existing Brain Trauma Foundation guidelines

suggest the use of intracranial pressure monitoring in specific patients after trauma (Level IIb)³, although there is evidence to suggest that this is variably practiced even at high-volume level I trauma centers^{19,20}. This may be in part due to the differences between techniques (ventricular drainage vs. parenchymal probes), anatomy (the presence of midline shift or slit-like ventricles), and practitioner preference. In any case, evidence is mounting that the measurement of ICP alone may be inadequate for the detection and mitigation of secondary brain injuries.

The insertion of multiple probes through a bolt provides a reliable way to monitor patients for the length of time required for critical care, and while dislodgement or discontinuation occurred frequently, this was in part related to patient transportation. After initial experience, additional safeguards included in the current protocol were implemented, such as strain relief measures. By way of contrast, tunneled probes may be more susceptible to traction and dislodgement because the length of the probes does not allow for the subgaleal fixation used to keep EVDs *in situ*. Some have argued that tunneled probes may be beneficial and can be adequately secured in order to avoid magnetic resonance imaging (MRI) incompatibility and artifacts, but many probes are not MRI compatible regardless of fixation²¹. Importantly, the use of multimodality monitoring is designed to provide time-resolute data during the acute period in which many patients are unstable to travel to MRI. Patients described here underwent monitoring within a median of 12.5 h and were monitored for a median of 4 days after trauma, which allowed for advanced imaging within a reasonable time frame.

The use of a single cranial access point reduces procedural risk, and strict patient entry criteria limits the potential for medication- or coagulopathy-related complications. The rates of minor hemorrhage reported here were in line with the documented incidence of peri-probe hemorrhages in the EVD literature^{22, 23}, although these are not uniformly reported. The rates of significant hemorrhage using the method described here are lower than those reported in the EVD literature and only slightly higher than the rates of significant hemorrhage associated with single intraparenchymal monitors. In addition to a relatively low overall operative risk, the use of a single, standardized burr hole is a bedside procedure, which allows this technique to be carried out in critically ill patients too unstable to move to an operative suite and by practitioners with bedside procedural privileges, such as neurosurgery house staff or neurointensivists.

There are several limitations that arise using a single burr hole placed at Kocher's point for neuromonitoring. First, the size of the burr hole and the use of a bolt preclude the placement of additional monitors, such as strip electrodes used as the gold standard for the detection of spreading depolarizations according to recommendation from the co-operative studies on brain injury depolarizations (COSBID) collaborative²⁴. Second, the spatial resolution of intraparenchymal monitoring may not be adequate to detect the signatures of secondary brain injury that occur remote from the probes. While the majority of the time monitors were placed near injured cortex, this approach is limited to frontal lobe monitoring, which may miss lesion development or evolution, for instance, in temporal or parietal cortex. Although this approach does not provide a global assessment of brain tissue, the ability to continuously monitor a vulnerable brain region provides the advantage of real-time patient care decision making.

The method presented here is flexible in allowing for multiple probes based on the equipment available to local sites. For instance, probes that measure microdialysis may be added to the fourth port available *via* the bolt without substantially modifying the existing protocol. Similarly, probes may be excluded if necessary.

In conclusion, a technique for multimodal monitoring after acute brain injury using a single bedside burr hole is described. This technique is flexible, provides reliable, clinically-actionable data that can be used by neurosurgeons and neurointensivists at the bedside within hours of injury.

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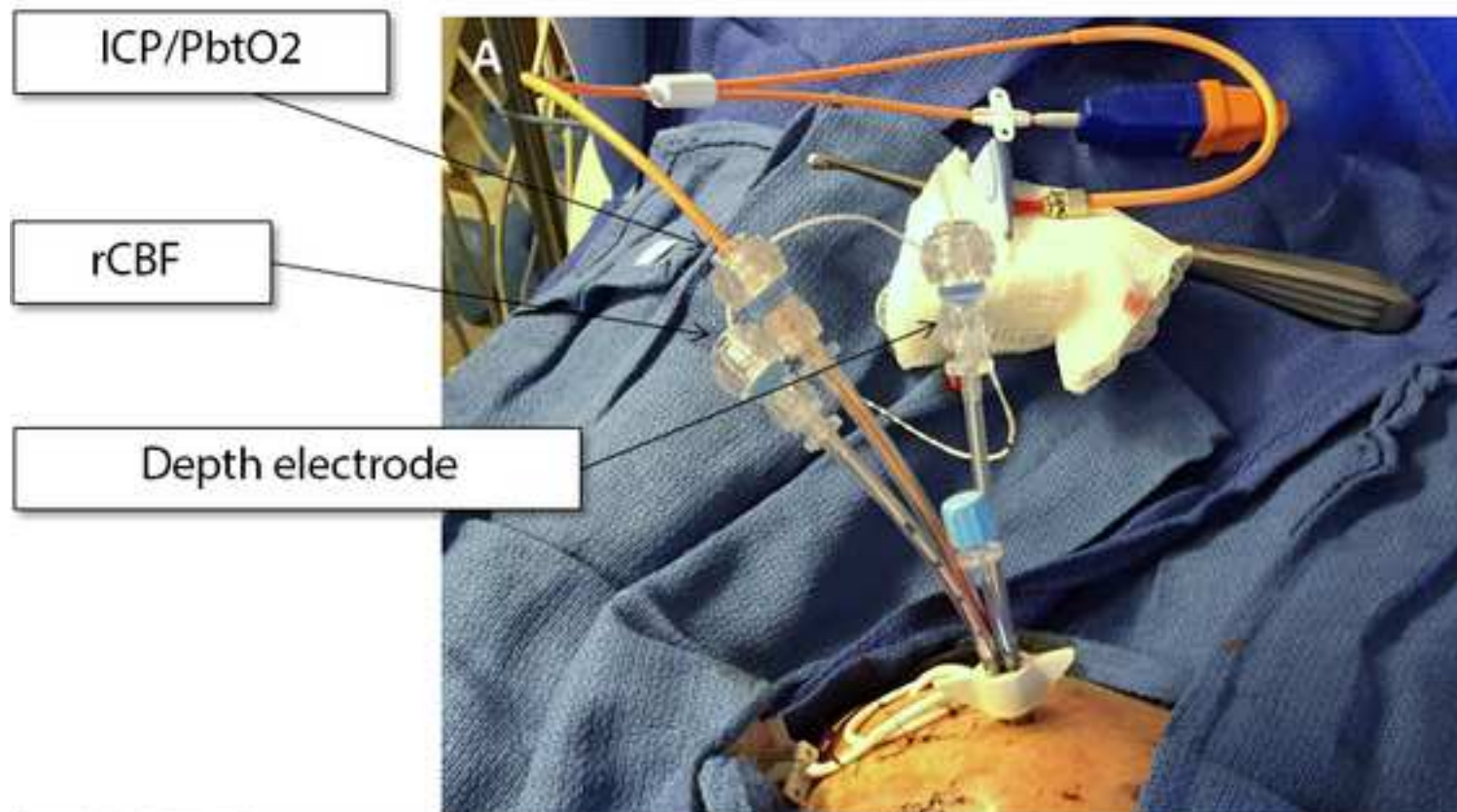
DISCLOSURES:

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Equipment	Measurement	Method of Measurement	Sampling Resolution
Quad lumen bolt kit	NA	NA	NA
ICP/PbtO2 probe	ICP	Mini-strain guage	125 Hz
	PbtO2	Fiberoptic	125 Hz
	ICT	Thermistor	NA
rCBF probe	rCBF	Distal thermistor	1 Hz
	ICT	Proximal thermistor	1 Hz
	K	Distal thermistor	per recalibration
Depth electrode	EEG	Platinum electrodes	≥ 256 Hz
70 Microdialysis bolt catheter	Lactate, pyruvate, glucose	Enzymatic measurement of interstitial	Hourly

Name of Material/ Equipment	Company	Catalog Number	Comments/Description
	Integra		
Cranial Access Kit	LifeSciences	NA	Cranial Access kit
Neurovent PTO	Qflow 500	NA	ICP/PBtO2 catheter
Qflow 500 Perfusion Probe	Hemedex, Inc	#H0000-1600	rCBF catheter
Qflow 500 Titanium Bolt	Hemedex, Inc	#H0000-3644	Cranial access bolt
Spencer Depth Electrode	Ad-Tech Medical Instr	NA	iEEG



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APPROVE, CURE OR HARM? ANNOTATE & MITIGATING HARMFUL & FAVORABLE VIDEO

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Editorial comments:

Changes to be made by the Author(s) regarding the written manuscript:

1. Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues.

Response: This is completed.

2. Affiliations: Please provide the full postal address of each affiliation.

Response: This has now been added to lines 6-11 on the title page.

3. Please provide an email address for each author.

Response: This is now included in the title page

4. Please include an ethics statement before the numbered protocol steps, indicating that the protocol follows the guidelines of your institution's human research ethics committee.

Response: The following was added to the paper on page 2:

This protocol was developed as a standard of care within our institution. The retrospective use of data gathered during the course of care was approved through a waiver of informed consent by the University of Cincinnati's Institutional Review Board.

5. Please revise the protocol text to avoid the use of any personal pronouns (e.g., "we", "you", "our" etc.).

Response: Text has been revised.

6. Please revise the protocol to contain only action items that direct the reader to do something (e.g., "Do this," "Ensure that," etc.). The actions should be described in the imperative tense in complete sentences wherever possible. Avoid usage of phrases such as "could be," "should be," and "would be" throughout the Protocol. Any text that cannot be written in the imperative tense may be added as a "Note." Please include all safety procedures and use of hoods, etc. However, notes should be used sparingly and actions should be described in the imperative tense wherever possible.

Response: Edits were made to focus on the imperative tense.

7. 1.1.1, lines 100-107: Please write the text in the imperative tense.

Response: This has been edited and included as part of 1.2:

Patients are excluded if they exhibit command following or if they cannot follow commands due to aphasia and have eye opening spontaneously or to voice.

8. Line 127: Please note that the items listed in 3.1.2.1-3.1.2.5 do not correspond exactly to those listed in Table 1. Please revise.

Response: Both the text and the table have been revised accordingly.

9. 7.2 and sub-steps (lines 187-216): Please write the text in the imperative tense.

Response: This has been revised, how lines 185-216.

10. Lines 190-191: Please describe in detail how to Raumedic intracranial pressure data.

Response: As detailed in step 7.2, equipment will vary. The Raumedic ICP data can be plugged into a bedside monitor or another monitoring device and data capture steps are outside of the scope of this manuscript.

11. Lines 192-201: The Protocol should be made up almost entirely of discrete steps without large paragraphs of text between sections. Please simplify the Protocol so that individual steps contain only 2-3 actions per step and a maximum of 4 sentences per step. Use sub-steps as necessary.

Response: This has been broken up into sections with a “Note” for text that is meant to be explanatory.

12. Lines 202-211: The Protocol should be made up almost entirely of discrete steps without large paragraphs of text between sections. Please mention how to measure cerebral blood flow. Please move the discussion about the protocol to the Discussion.

Response: This has been broken up into sections with “Notes” for the larger text sections that are required for troubleshooting, but outside of the scope of the Discussion (which is more about the operative surgical technique). At the Editors discretion, data verification may be omitted if it detracts from the discrete operative steps described in prior sections.

13. At the end of the procedure, please mention how the patients are treated for any pain or recovery.

Response: The following section was added to address pain and recovery:

8. Patient Care

8.1 *Following the procedure, no further pain control is necessary and no prophylactic antibiotics are required.*

8.2 *At the end of the clinical monitoring period, remove the bolt by first removing each of the probes individually. Then, twist the bolt counterclockwise until it comes loose from the skull and can be removed.*

8.3. *Use sterile technique to suture the skin opening and monitor for any cerebrospinal fluid leakage, bleeding, or swelling at the site.*

14. Please include single-line spaces between all paragraphs, headings, steps, etc.

Response: Completed; paragraphs are denoted by indentation now.

15. After you have made all the recommended changes to your protocol (listed above), please highlight 2.75 pages or less of the Protocol (including headings and spacing) that identifies the essential steps of the protocol for the video, i.e., the steps that should be visualized to tell the most cohesive story of the Protocol.

Response: This is now highlighted in yellow.

16. Please highlight complete sentences (not parts of sentences). Please ensure that the highlighted part of the step includes at least one action that is written in imperative tense. Please do not highlight any steps describing anesthetization and euthanasia.

17. Please include all relevant details that are required to perform the step in the highlighting. For example: If step 2.5 is highlighted for filming and the details of how to perform the step are given in steps 2.5.1 and 2.5.2, then the sub-steps where the details are provided must be highlighted.

Response: Areas have been highlighted in the Revised text.

18. Figure 1 and Table 1: Please remove commercial language including trademark symbols (™), registered symbols (®), and manufacturer/product names (Neurovent®, Qflow 500™, Spencer®).

Response: This is done in both Figure 1 Revised and Table 1 Revised.

19. Discussion: Please describe critical steps within the protocol.

Response: If the Editor would provide additional guidance, I would be happy to include critical steps within the discussion. All steps are described within the protocol and non-imperative information is primarily discussed with regard to feasibility and safety in the Discussion.

20. Please revise the table of the essential supplies, reagents, and equipment to include

the name, company, and catalog number of all relevant materials in separate columns in an xls/xlsx file. Please remove trademark (™) and registered (®) symbols.

Response: This is done per comment 18. Catalog numbers are not available for some devices and are not necessarily relevant to this list but the name of supplies, company, and even information about the sampling frequency of the devices is included.

Reviewer #1:

Manuscript Summary:

Foreman and colleagues have succinctly and nicely described the role of invasive intracranial multimodality monitoring following acute brain injury, such as TBI and stroke, and provided a thorough, yet easily followed, protocol for the bedside placement of multiple intraparenchymal monitors, such as ICP, PbtO₂, CBF, EEG depth electrodes, and (optionally) microdialysis. The protocol is similar to that used at several institutions well-known for their multimodality monitoring programs, however, as yet I am unaware of a published protocol that summarizes the benefits, patient selection, and steps in monitor placement as evidenced by this manuscript.

Major Concerns:

None.

Minor Concerns:

Some minor edits and/or additions could be considered to the protocol:

1. Technically, I would describe the technique as a twist drill craniostomy, rather than a burr hole, as traditionally a burr hole is somewhat larger in diameter (~1-1.4 cm). These are relative semantics, however, and seems the terms are frequently used interchangeably nowadays.

Response: The reviewer raises a good point, and the following was added to the introduction to make it clear that the terms are being used interchangeably, as per modern parlance.

...introduced through a twist drill craniostomy (often referred to interchangeably as a burr hole) (lines 52-53)

2. Lines 154-155: While some practitioners prefer a scalpel blade to incise the dura, others (particularly those using other cranial access kits), may find that the scalpel blade is too large or not particularly conducive to this when a small twist drill craniostomy is used. Another technique commonly employed is to perforate the intact dura several times with an 18-gauge needle using tactile feedback until the dura is sufficiently opened.

Response: In order to allow flexibility for individual technique, the following note was added to 4.5:

Note: Some practitioners may use alternative approaches, such as using an 18-gauge needle to perforate the dura using tactile feedback until the dura is sufficiently opened. Adequate durotomy is critical regardless of the technique, and incomplete durotomy may lead to difficulty passing thin, flexible catheters or malpositioning of the catheters.

3. Line 173: The word "tape" is misspelled as "table".

Response: This has been corrected.

4. Lines 176-177: Another option is to wrap a thin strip of xeroform gauze around the base of the bolt housing where it comes in contact with the skin. This provides a barrier to infection and is also bacteriostatic.

Response: This was added to Section 6.4:

Optional: Use a large 6"x2" tegaderm or a thin strip of xeroform gauze to wrap the base of the bolt, reducing the exposure of the skin-to-burr-hole interface. Xeroform gauze also provides bacteriostatic function.

5. Lines 202 and 212: The section number 7.1.2 is inadvertently repeated. The sections on Cerebral Blood Flow and Depth EEG should be renumbered to 7.1.3 and 7.1.4, respectively.

Response: The numbering in this section required editing and now should be accurate.

6. Line 294: Change the word "adequate" to "adequately".

Response: This has been edited.

Reviewer #2:

In this observational, single center study, the authors described the method of recording multimodality monitoring signals in patients with severe traumatic brain injury via single Burr hole placement. The study describes a technique that allow the simultaneous placement of multiple modality probes that measure ICP, PbtO₂, rCBF and iEEG in hopes of targeted monitoring of multiple physiological parameter in hopes of mitigating secondary brain injuries. The authors described a patient cohort of forty three patients who underwent invasive multimodality monitoring using a pre-determined standardized protocol. This well designed study showed merit but had limitation and weakness.

Specific Comments:

1. The major weakness of the study in my opinion is that despite the invasive nature of the procedure, Multimodality monitoring still does not provide a global assessment of

brain tissue as the probes only provide localized assessment of brain tissue. A PET scan or MRI might provide such assessment but having a ICP bolt might preclude patients from having this neuroimaging modality as most of the ICP Bolts monitors are not compatible. This might cause a delay in patient care who might have benefited from neuroimaging sooner.

Response: Our intent with this manuscript is to describe a technique that allows for continuous measures of brain physiology. We acknowledge that imaging exhibits better spatial resolution and provides important complementary information, but a full discussion of the differences in modalities is beyond the scope of this manuscript. However, we have added some text to our discussion to address the important limitation that multimodality monitoring does not provide an assessment of global brain tissue. Our technique is performed during the acute period (a median of 12.5 hours following injury) when patients are often unstable to travel to PET or MRI scans. However, there were several patients in this cohort who underwent urgent MRI to gauge the extent of diffuse axonal injury prior to bolt placement, so this procedure does not preclude imaging assessments in appropriate patients. Finally, our median monitoring duration was only 4 days, allowing for PET or MRI testing as needed within a week of injury, and in time for prognostic decision-making.

I have added the following to the Discussion (pg 6):

Importantly, the use of multimodality monitoring is designed to provide time-resolute data during the acute period in which many patients are unstable to travel to MRI. Patients described here underwent monitoring within a median of 12.5 hours and were monitored for a median of 4 days after trauma, which allowed for advanced imaging within a reasonable time frame.

I have also added the following to the Discussion (pg 8):

Although this approach does not provide a global assessment of brain tissue, the ability to continuously monitor a vulnerable brain region provides the advantage of real-time patient care decision making.

2. The other concern is that the authors failed to describe the patient selection process that they used in their decision making. I commend them for doing a great job in detailing their methods but a useful guide should include patient selection process and potential complications.

Response: Patient selection is likely to be site specific, but we agree this is an important aspect to deploying this or similar protocols. We included a sample protocol in our recent publication (Foreman, B., Ngwenya, L.B., Stoddard, E., Hinzman, J.M., Andaluz, N., Hartings, J.A. Safety and Reliability of Bedside, Single Burr Hole Technique for Intracranial Multimodality Monitoring in Severe Traumatic Brain Injury. *Neurocritical Care*. doi: 10.1007/s12028-018-0551-7 (2018)) which is referenced within the text, and included the following in 1.2:

Patients are excluded if they exhibit command following or if they cannot follow commands due to aphasia and have eye opening spontaneously or to voice.

Complications are mentioned in 1.3 and discussed in detail within the Discussion. I would be happy to address specific complications further with guidance from the Reviewer.

3. Despite the above limitations, I feel that this is a well-designed study. I commend the authors for taking the initiative in trying to solve the mystery of brain monitoring which still remains a "black box." I would recommend that the authors expand this to a multi-center study in hopes of creating a comprehensive protocol.

Response: We share the Reviewer's optimism that this can be performed across multiple centers and have been working with others who have employed a similar procedure successfully. By standardizing this procedure, we hope that patient safety, data quality, and clinical management are positively impacted.

Sincerely,

Brandon Foreman, on behalf of the authors