STUDY PROTOCOL

DUAL ICP STUDY

Intracranial Supra- and Infratentorial Multimodal Neuromonitoring

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ABSTRACT

Invasive neuromonitoring of intracranial pressure (ICP) is an important element of neurosurgical critical care that is used primarily as an indicator of adequate cerebral perfusion in patients, when clinical observation is not an option. Due to the constraint in size and the critical structures within the posterior fossa, detection of intracranial pressure particularly in the postoperative phase has been deemed desirable in patients with surgery in this region, particularly in those subjected to prolonged procedures and critical care.

The posterior fossa is an anatomically constricted compartment with narrow spaces and intracranial hypertension quickly leads to brainstem damage and neurological dysfunction. ICP in the supratentorial space not necessarily correlates with ICP in the infratentorial space. Some authors claim that it would be beneficial to measure ICP in infratentorial space after posterior fossa surgery in some cases.

In patients whose neurological examination results may be inconclusive or limited, it is valuable to have a reliable alternative method of evaluation. It is generally accepted that continuous ICP monitoring is very important to determine the timing of surgery and to prevent secondary brain damage caused by increased ICP.

The relationship between the intracranial pressure (ICP) profiles in the supratentorial and infratentorial compartments remain unclear. After a neurosurgical operation in the posterior fossa there are most likely pressure differences between supra- and infratentorial spaces. It is well known that the pressure within the skull is unevenly distributed, with appreciable ICP gradients. To rely on autonomic changes or neurological deterioration as signs of a postoperative complication narrows the temporal margin of safety for the institution of treatment.

It has been the policy of our Department to electively monitor all complex posterior fossa procedures via a supratentorial intracranial multimodal monitoring; however, it remains unclear whether an acute change in the posterior fossa would be reflected by the supratentorial monitor prior to clinical deterioration.

Thus, we intend to apply the intracranial multimodal monitoring in both infratentorial and supratentorial compartments simultaneously. Such coincident measurements most likely will be the most sensitive way to assess focal swelling, ischemia and tissue perfusion, or other relevant complications in the posterior fossa structures.

The goal of this study is to test whether direct infratentorial monitoring is a more efficacious method for detecting dynamic changes in the operative compartment and whether it is safe, in view of the critical structures within the region. In particular, the motivation behind this study is also to determine the value of ICP and brain tissue oxygenation monitoring (LICOX) in the infratentorial compared to the supratentorial space in patients with posterior fossa lesions. We aim to immediately detect any pertinent complications that are related to mass effect or swelling within the posterior fossa, resulting in subsequent prompt therapeutic intervention in these patients. With this in mind, postoperative multimodal neuromonitoring is a standard procedure at our intensive care unit. The additional intracranial infratentorial monitoring most likely is the most sensitive way to detect any relevant complications or lesions that may result in irreversible sequelae.

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INTRODUCTION AND GOALS

BACKGROUND

CRANIAL LESIONS IN THE POSTERIOR FOSSA AND INTRACRANIAL MULTIMODAL NEUROMONITORING

Invasive neuromonitoring of intracranial pressure (ICP) is an important element of neurosurgical critical care that is used primarily as an indicator of adequate cerebral perfusion in patients, when clinical observation is not an option. Due to the constraint in size and the critical structures within the posterior fossa, continuous detection of postoperative pressures has been deemed desirable in patients with surgery in this region, particularly in those subjected to prolonged procedures and critical care.

The posterior fossa is an anatomically constricted compartment with narrow spaces and intracranial hypertension quickly leads to brainstem damage and neurological dysfunction. ICP in the supratentorial space not necessarily correlates with ICP in the infratentorial space. Some authors claim that it would be beneficial to measure ICP in infratentorial space after posterior fossa surgery in some cases.

In patients whose neurological examination results may be inconclusive or limited, it is valuable to have a reliable alternative method of evaluation. It is generally accepted that continuous ICP monitoring is very important to determine the timing of surgery and to prevent secondary brain damage caused by increased ICP.[1, 2]

There have been few clinical studies in which simultaneous pressures were recorded above and below the tentorium in patients with intracranial pathology. Smyth and Henderson[3] found a lower lumbar pressure in 8 of 33 patients with intracranial space-occupying lesions, most of which were tumors, but the maximum difference in pressure was 100 mmH_20. Yet, these findings together with a statement by Evans:[4] "We now know as a result of many observations that there is a close correspondence between the ventricular and lumbar pressures under almost all circumstances" contrast with the high incidence of transtentorial herniation demonstrated post-mortem in patients with brain tumors.[5]

Developing and improving methods to monitor patients with posterior fossa lesions and to evaluate efficacy of treatment are essential. These include neuroimaging as well as intracranial multimodal neuromonitoring, mostly placed in the supratentorial compartment.

The relevance of infratentorial neuromonitoring remains largely unclear. So far, the placement of ICP probes in the posterior fossa seems to carry very low morbidity. Furthermore, to rely on autonomic changes, neurological deterioration, or measurements of only the supratentorial compartment as a sign of relevant complications in the posterior fossa highly narrows the temporal margin of safety for the institution of treatment. Comprehensive evaluation of possible risks of posterior fossa lesions and their treatments is crucial. Of note, immediate detection of treatment-related complications is often challenging, still being able to avoid permanent neurological sequelae. The application of the advanced neuromonitoring in the posterior fossa may be supportive in achieving this difficult goal and may provide objective assessments of procedure-related complications.

Therefore, the data generated by the above-mentioned method can be expected to be beneficial in individualized treatment plans.

It is a relatively novel approach to intracranial multimodal neuromonitoring. The application of infratentorial probes offers potential for better understanding of lesion maturation and progression, clinical deterioration, and monitoring the effect of treatments.

We hypothesize that additional multimodal infratentorial neuromonitoring will be of high clinical value detecting any relevant complication and giving detailed insight in pathophysiological interactions in posterior fossa lesions.

HISTORY

In the late 19th century, a widespread interest evolved in the problem of cerebral compression and the etiology of neurological deficits induced by an expanding intracranial mass. As methods were developed for recording intracranial and intraspinal pressure and for the experimental production of acute intracranial hypertension, it was observed by some investigators[6-10] that increased pressure was not transmitted consistently from the intracranial to the intraspinal space.

With regard to communication of pressure within the brain, von Bergmann[11] was the first as early as 1885 to conclude from experimental studies that the brain does not transmit pressure equally in all directions. In 1901, Cushing[7] stated that the pressure exerted by an intracranial foreign body "is not transmitted equally throughout the cerebral chamber, and in consequence the circulatory embarrassment in corresponding degrees is unevenly felt." He also affirmed that severe effects of compression could occur locally with little or no transmission to remote areas of the brain. Meyers[8] also found such a differential with injection of Ringer's lactate into the lateral ventricle, but the gradients of pressure illustrated in these papers were relatively small. More recently, Kahn[9] produced experimental increased intracranial pressure by perfusion of distilled water into the common carotid artery and found that a differential of pressure developed between the supratentorial space and the posterior fossa. Penn[12] and Leech and Miller[13] also found such a differential with injection of Ringer's lactate into the lateral ventricle, but the gradients of pressure illustrated in these papers were relatively small.

Clinical interest in the transmission of increased intracranial pressure developed as a result of the demonstrated importance of transtentorial herniation causing rapid neurological deterioration and death in patients with a space-occupying intracranial mass. This was reemphasized by Finney and Walker.[5] They found evidence of transtentorial herniation in 55.4% of an unselected series of brain tumor autopsies, including an incidence of 88% in glioblastomas of the cerebral hemisphere. In 23% of supratentorial tumors herniations of both tentorial incisura and foramen magnum were present.

Clarifying the high incidence of transtentorial herniation, Langfitt et al[10] postulated that since communication of pressure from the supratentorial space to the posterior fossa is dependent upon patency of the basal cisterns surrounding the brain stem in the tentorial incisura, an early manifestation of obstruction of the incisura is the development of a differential of pressure between the supratentorial and infratentorial spaces.

In their initial experiments[10] a balloon was placed in the extradural space in the posterior fossa in order to create a space-occupying mass, but with gradual inflation of the balloon stripping of the dura mater from the skull over the transverse sinus occurred, and the balloon expanded into the supratentorial space. Therefore, the infratentorial balloon was inserted in the subdural space over the lateral and inferior aspects of the cerebellum.

It is worthy of notice that a failure of communication of pressure from the infratentorial to the supratentorial space then occurred with inflation of the balloon. With small volumes of the balloon the intracerebral pressure was elevated to several times the subarachnoidal pressure over the corresponding cerebral hemisphere, and communication of pressure to the subarachnoidal space occurred gradually as the intracerebral mass was enlarged with additional injections. In contrast, transmission of pressure from the subarachnoidal space through the brain to the intracerebral balloon was invariably complete and virtually instantaneous.

In prior experiments[14-16] performed by the Philadelphia group in which sustained increased intracranial pressure was produced by a gradually expanding extradural mass, the pressure within the extradural mass was equal to the pressure in the opposite extradural space in some animals, whereas in others it was many times the contralateral extradural pressure. This demonstrated that the dura mater can restrain significantly the expansion of an extradural mass and prevent transmission of pressure from the mass to the underlying brain.[14] Likewise, it was found that a progressive failure of communication of pressure from the supratentorial to the infratentorial space occurs as cerebral tissue obstructs the tentorial incisura, and herniation of the cerebellar tonsils into the foramen magnum prevents transmission of pressure from the posterior fossa to the spinal canal.[10] Thus, in these circumstances the brain does not transmit increased intracranial pressure.[10]

With the gradual expansion of an extradural mass, transmission of pressure from the mass to the brain is dependent upon the firmness of attachment of the dura mater to the inner table of the skull, its configuration in relation to the underlying brain, and its physical properties.[17]

In the past, recording of ventricular fluid pressure has proved to be a reliable method in clinical neurosurgery, as shown by Lundberg et al.[18-20] Furthermore, some authors recorded supratentorial pressure during posterior fossa surgery with the intention of obtaining continuous information on the pressure state in major intracranial compartment.[3, 21, 22]

Of note, some surgeons were reluctant to introduce direct subdural posterior fossa monitors for a number of reasons. Some of the possible problems may include cerebrospinal fluid (CSF) leaks, cranial nerve dysfunction, and the possibility of brainstem irritation with resulting autonomic dysfunction. Yet, many recent studies have showed the safety and feasibility of intracranial monitoring in the posterior fossa.[1, 21, 23-26]

PRESENT

With regards to pathophysiology and clinical practice, the intracranial pressure (ICP) profiles in the supratentorial and infratentorial compartments remain unclear. After a neurosurgical operation in the posterior fossa there are most likely pressure differences between supra- and infratentorial spaces.[27] It is well known that the pressure within the skull is unevenly distributed, with demonstrated ICP gradients.[25] By contrast, Rieger et al[23] reported no significant differences between supratentorial and infratentorial ICP values in an animal model. The infratentorial ICP elevation in the presented pig model led to a uniform ICP elevation in the intracranial space without development of a considerable pressure gradient below and above the tentorium. Importantly, in the low pressure part of the ICP curve, cerebrospinal fluid connects the compartments and contributes to the pressure equilibrium.

To rely on autonomic changes or neurological deterioration as signs of a postoperative complication narrows the temporal margin of safety for the institution of treatment.

It has been the policy of our Department to electively monitor all complex posterior fossa procedures via a supratentorial intracranial multimodal monitoring; however, it remains unclear whether an acute change in the posterior fossa would be reflected by the supratentorial monitor prior to clinical deterioration.

Thus, we intend to apply the intracranial multimodal monitoring in both infratentorial and supratentorial compartments simultaneously. Such coincident measurements most likely will be the most sensitive way to assess focal swelling, ischemia and tissue perfusion in the posterior fossa structures.

Importantly, the benefits of intracranial pressure (ICP) monitoring must be weighed against the associated risks and complications. The risks of ICP monitoring are related to the degree of invasiveness, the location of the device, the presence of systemic infections, the need to restrict patient movement, and monitoring drift or artificially low readings. Complications include infection, hematomas, epilepsy, cerebral puncture, cranial nerve palsies, and CSF leaks. In general, the incidence of complication has been quoted as from 1.1% to 7.7%.[28-32]

A major motivating factor in our routine use of postoperative ICP monitoring is that clinical parameters (for example, blood pressure, neurological status, pulse, and respiration) are not always reliable markers of increased ICP or impending neurological deterioration secondary to complications.[10, 33] Moreover, some authors have showed the safety of ICP monitoring in the posterior fossa.[1, 21, 23-26]

AIMS OF THE STUDY

The goal of this study is to test whether direct infratentorial monitoring is a more efficacious method for detecting dynamic changes in the operative compartment and whether it is safe, in view of the critical structures within the region.

The motivation behind this study is to determine the value of ICP and brain tissue oxygenation monitoring (LICOX) in the infratentorial compared to the supratentorial space in patients with posterior fossa lesions. Our aim is also the immediate detection of any pertinent complications that are related to mass effect or swelling within the posterior fossa, leading to subsequent prompt intervention in these patients. With this in mind, postoperative multimodal neuromonitoring is a standard procedure at our intensive care unit. The additional intracranial infratentorial monitoring most likely is the most sensitive way to detect any relevant complications or lesions that may result in irreversible sequelae.

The additional monitoring may also help to direct normal postoperative care in terms of ventilatory support, the use of positive end-expiratory pressures, continued osmotherapy, and patient positioning. Finally, in postoperative patients with a neurological deficit or in those who must be maintained sedated or paralyzed, ICP- and brain tissue oxygenation (LICOX) with blood pressure monitoring are highly reliable methods to detect potential worsening as soon as possible. Of note, the infratentorial and supratentorial compartments are related by conduction of fluid in the subarachnoid space.

Under normal anatomical conditions, there is little intercompartmental difference in pressure between the infra- and supratentorial fossae. Surgery, brain shifts, or occlusion of the basilar cisterns may radically alter the equilibration of both compartmental pressures, since brain is a non-Newtonian fluid.[33] Furthermore, the pressure and compliance within the two compartments are different, as indicated by aforementioned studies.[7-9, 12, 13, 25] A thorough review of the current literature reveals little information concerning the specific risks and complications related to direct posterior fossa monitoring, and just fractional knowledge of ICP pathophysiology in the posterior fossa and relations between both supra- and infratentorial compartments.

Ultimately, recent data[1, 21, 23-26] strongly support the thesis that infratentorial monitoring is a safe technique, and most likely does not offer any greater risk than a subdural catheter located in the supratentorial space. In addition, the placement of the monitor within the operative site prevents exposing the patient to double jeopardy for infection, by avoiding a separate procedure. It is well known that the risk of infection is greatest at the time of introduction of any ICP monitoring device.

To summarize all intentions of the anticipated clinical trial we aim to:

1) prove the safety and feasibility of the intracranial multimodal monitoring in the posterior fossa,
2) establish the methodological use of infratentorial multimodal monitoring in patients with posterior fossa lesions as standard of care;
3) gain additional information of posterior fossa pathophysiology with complementary monitoring of the dynamical changes; subsequently
4) facilitate the neurointensive care of these patients including ventilatory support, the use of positive end-expiratory pressures, continued osmotherapy, and patient positioning; ultimately
5) better understand of pathophysiological processes with
6) immediately identify of complications with subsequent prompt intervention if needed.

QUESTIONS

* Is infratentorial multimodal neuromonitoring safe and feasible, and necessary?
* Do data assessed by multimodal monitoring in the posterior fossa correlate with data from the supratentorial compartment?
* Is infratentorial multimodal neuromonitoring able to timely predict complications such as local swelling, mass effect, vasospasm, ischemia, or infarction?
* Is infratentorial multimodal neuromonitoring of value in daily clinical practice?

HYPOTHESES

- The intracranial multimodal monitoring in the posterior fossa is safe and feasible, without any increased risk due to additional probes.
- Data generated by infratentorial multimodal neuromonitoring do not completely correlate with data from standardized supratentorial multimodal neuromonitoring. There are significant differences in ICP- or brain tissue oxygenation values between the supratentorial and infratentorial compartments.
- The infratentorial multimodal monitoring immediately detects all relevant complications related to posterior fossa lesions including mass effect, local swelling, postoperative hematoma, ischemic events, decrease in the blood flow, vasospasm and inadvertent or prolonged vessel occlusion, or infarction, resulting in prompt therapeutic intervention if necessary.
- Additional information from infratentorial probes facilitate to maintain the critical patients including ventilatory support, the use of positive end-expiratory pressures, continued osmotherapy, and patient positioning.

CLINICAL RELEVANCE

Our prospective study can provide better guidance and optimization of clinical therapy through a comprehensive assessment of patients harboring posterior fossa lesions.

This study has very high potential to generate a new intellectual property, to yield discoveries improving the prediction of complications and monitoring the effects of treatments. The data will offer better understanding of pathophysiological mechanisms in posterior fossa lesions.

STUDY DESIGN

METHODS

In phase I of the study 15 patients with posterior fossa lesions who require prolonged neurointensive care and in which any intracranial invasive intervention is indicated regardless of used technique or treatment modality will be enrolled in the study. The indication for posterior fossa lesion treatment will be decided on a case-by-case basis by our neurosurgical team irrespective of the study.

The study will start as a monocentric clinical trial (pilot study), and subsequently in phase II the study is planned to be continued as a multicentric trial.

In the majority of patients, ICP- and LICOX sensors are usually placed in the right frontal lobe and/or at the site of the lesion. In case of posterior fossa surgery, additional probes (ICP / LICOX) will be placed into the surgical field.

The neuromonitoring data will be recorded and analyzed. Additionally, demographic data, all treatment-related complications, and management of intracranial hypertension will be recorded.

All adverse effects will be noted and reported, even if no clinical consequence will ensue. Non-neurological complications such as cardiopulmonary complications will be documented separately.

After the invasive treatment of the posterior fossa lesion, all patients will undergo CT and/or MRI as standard of care within 72 hours after the intervention (the acute phase) as a protocol for detection of procedure-related complications. As standard of care, an additional follow-up MRI will be performed if needed. In stable patients a preoperative MRI will also be performed before invasive treatment

The following outcomes will be evaluated and analyzed: mean ICP, ICP pulse amplitude, respiratory waves, slow waves and the RAP (compensatory reserve) index of supra- and infratentorial ICP signals, transtentorial difference, brain tissue oxygenation, blood saturation, ASTRUP, and further vital parameters, peri- and postoperative morbidity and mortality, procedure-related morbidity including infection, hematomas, epilepsy, cerebral puncture, cranial nerve palsies, and CSF leaks, perioperative cerebral ischemia, long-term neurological morbidity and mortality, and overall neurological outcome.

Institutional review board will be obtained by the Ethics Committee of the Medical University Innsbruck, Austria. Informed consent will be acquired from all patients for participation in the study during the study period according to local requirements.

All treatment techniques and MRIs will be performed as a part of routine clinical care and no modifications will be introduced in the treatment or the follow-up modalities currently used by the Department of Neurosurgery and Neuroradiology, with the exception of ^{31}P- MRS (see above).

VARIABLES AND PARAMETERS

Clinical data

The following demographic characteristics of treated posterior fossa lesions and outcomes will be documented and analyzed: type, location, size, shape, volume, technical success of treatment, recurrence, bleeding / rebleeding, perioperative morbidity and mortality, procedure-related morbidity including thromboembolic events, iatrogenic rupture, perioperative stroke, occurrence of complications related to lesion (e.g. mass effect, delayed ischemia, hydrocephalus, vasospasm, etc.) long-term neurological morbidity and mortality, and overall good neurological outcome

Cerebral multimodal neuromonitoring

ICP, brain oxygen partial pressure (PtO_2) / **LICOX**®, alternatively microdialysis, cerebral blood flow / **Hemedex**®, cortical spreading depolarization (CSD)

MRI (including DWI and ^{31}P-MRS in selected cases)
Phosphocreatin (PCr), Phosphomonoester (PME), Phosphoethanolamin (PEth), Phosphocholin (PCho), Phosphodiester (PDE), Glycero-Phosphocholin (GPC), Glycero-Phosphoethanolamin (GPE), Anorganisches Phosphat (Pi), Adenosin-Triphosphat (α, β, γ ATP), Adenosin Diphosphat (ADP), Mg^{2+}, pH

INTERVENTION/EXAMINATION

All patients suffering from symptomatic posterior fossa lesions are first treated and stabilized in the emergency room and/or at the ICU. After the initial imaging (in most cases CT/CTA), if necessary, patients are transported to the OR and/or the angiosuite. After treatment, regardless of the used treatment modality and possibly after implementation of invasive multimodal neuromonitoring according to contemporary guidelines by patient impaired consciousness (e. g., with GCS≤8), implantation of multimodal neuromonitoring is performed – please find the details in the study protocol TIBI-study (AN2014-0201 339/4.6 – microdialysis, tissue perfusion measurement, ICP-measurement, LICOX) the patients are transported to the neurosurgical or neurological ICU. In each patient, MRI including ^{31}P-MRS will be performed at different stages of treatment (the indication for neuroimaging will be decided on a case-by-case basis). As mentioned above, in stable patients a preoperative MRI will also be performed which may provide additional relevant information for patient treatment.

Simultaneously, data from invasive multimodal neuromonitoring and laboratory values will be acquired and evaluated during the ICU stay after treatment.

All methods are validated by an international collaborative ring trial, as they are used in routine.

Finally, outcome scores like the mRS and the Glasgow Outcome Scale will be recorded.

INSTRUMENTS

- ***Multimodal Neuromonitoring***

- ☐ ICP-measurement, Raumedic, Münchberg, Germany
- ☐ Brain tissue oxygen and brain temperature, Licox, Integra, Plainsboro, New Jersey, USA
- ☐ Cerebral microdialysis, CMA, Stockholm, Sweden
- ☐ Alternatively tissue perfusion measurement, Hemedex, Cambridge, MA,USA

DISSEMINATION

A part of this study will most likely be assigned as a clinical Ph.D.-project for the residents at the Department of Neurosurgery.

STUDY POPULATION (SPECIMEN / TEST PERSON / PATIENTS)

IN- AND EXCLUSION CRITERIA

INCLUSION CRITERIA

- ☐ Posterior fossa lesions with anticipated prolonged neurointensive critical care
- ☐ Patients older than 18 years
- ☐ Informed consent if applicable (unconscious patients will be also enrolled)
- ☐ No existing exclusion criteria

EXCLUSION CRITERIA

- ☐ Coagulation disorders
- ☐ Age < 18 years
- ☐ Pregnancy

INFORMED CONSENT OF TEST PERSONS / PATIENTS

All patients harboring posterior fossa lesion who meet the inclusion criteria will be enrolled in the study.

Informed consent will be acquired from all patients for participation in the study during the study period.

All interventions and neuroimaging (e.g. MRI) will be performed as a part of routine clinical care and no modifications will be introduced in the treatment or the follow-up modalities currently used by the Department of Neurosurgery / Neuroradiology, except ^{31}P-MRS (see above).

CALCULATION OF THE NUMBER OF CASES

The study is designed as a prospective clinical trial (the sample of 30 patients was selected according to epidemiologic data and estimated annual incidence of posterior fossa lesions in Central Europe).

Regarding the complex patient cohort a high drop-out rate for MRI in the acute phase due to unstable patients with a consecutive infeasibility of MRI is to be expected.

ANALYSIS

Data collection

Clinical and procedural data will be collected prospectively. The adverse events are classified in three groups, according to their mechanism:

* Lesion-related events
* Intraoperative / intraprocedural (iatrogenic) events
* Device-related problems

The outcome of adverse events is classified in four groups:

* No clinical modification
* Transient deficit(s)
* Permanent deficit(s) (deficit(s) remaining at the 6-months follow-up)
* Death

All-cause morbidity is defined as a modified Rankin score ≥ 3. When the preoperative mRS was greater than 2, the all-cause morbidity is defined as any increase in the mRS value.

STATISTICAL ANALYSIS

The distribution of continuous variables will be described by using means and standard deviations, and discrete variables will be described as frequencies, percentages, and confidence intervals. The Clopper-Pearson exact method will be used to construct 95% confidence intervals (CIs).

The characteristics of both treatment groups will be compared by using Chi^2 test. All outcome results will be compared between the study groups by using a MannWhitneyU test, or Student t test where appropriate. $P < 0.05$ is considered indicative of a statistically significant difference.

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