Lumbar Puncture Before, During, and After Space Flight – Approach and Challenges

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We will mention off-label use and/or investigational use of non-invasive intracranial pressure measurement technologies in this presentation (slide #5).
Background

The leading pathophysiological hypothesis for the VIIP syndrome: Increase in intracranial pressure (ICP) due to microgravity-induced cephalad fluid shifts

Evidenced by:
- Imaging findings typical for elevated ICP (in-flight ultrasound, postflight MRI)
- Optic disc edema on fundoscopy and Optical Coherence Tomography (OCT)
- High opening pressure in 4 out of 5 crewmembers who underwent postflight lumbar puncture (LP) due to optic disc edema
ICP has never been directly measured in humans during microgravity exposures

- Russians have measured ICP invasively in two flown Macaque monkeys in the 1990s, and found mild elevations (25%) compared with preflight measurements, that never exceeded the normal physiological range

Verification of elevated ICP in-flight is required for validating the etiological hypothesis and developing countermeasures

Terrestrially, LP is the gold standard method to quantitatively measure ICP in ambulatory patients
NASA and the NSBRI are currently evaluating several technologies that allow noninvasive ICP measurement, however these technologies may be several years away from FDA approval and flight certification.

Consequently, rationale exists to consider pre- and postflight LP testing, and possibly in-flight testing, for both occupational monitoring and hypothesis-driven research.
NASA Crewmember LPs to Date

- LPs are not a part of the current nominal medical testing requirements before, during, or after space flight, and are done on a case-by-case basis only if clinically indicated.
- 5 LPs conducted postflight in crewmembers with clinical indication (optic disc edema).
- No preflight LP as baseline.
- LP exams were not standardized (done for clinical purposes).

<table>
<thead>
<tr>
<th>Case</th>
<th>Opening pressure (cm H₂O)</th>
<th>Time after flight (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>22</td>
<td>66</td>
</tr>
<tr>
<td>B</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>C</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>D</td>
<td>28.5</td>
<td>57</td>
</tr>
<tr>
<td>E</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
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Normal range 10-20 cm H₂O
Approach to Increasing LP Data

Safety
Risk analysis for pre/postflight and in-flight

Ethics
Mandatory vs. voluntary

Logistics

Implementation
Approach to Increasing LP Data

**Safety**
Risk analysis for pre/postflight and in-flight

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**Implementation**
Challenges – Safety Pre/Postflight

→ To address safety concerns for pre-/in-/postflight LP:
  • Review of the literature conducted
  • Subject matter experts consulted

→ An LP is a common procedure terrestrially for diagnostic and therapeutic indications

→ Low risk of complications
  • Considered a safe procedure when performed on Earth by experienced clinicians
  • The performance of pre- or postflight LPs on crewmembers carries the same risks as any other LP performed terrestrially
  • Some complications, if prolonged, may impact crewmember training → Feeds into timing of LP (logistics)
Challenges – Safety In-Flight

→ In-flight LP much more complex

→ Many unknowns regarding performance of such a procedure in microgravity → May increase the level of risk

→ Safety aspects to consider in-flight include:
  * Risk of infection
  * Microgravity-associated anatomical and physiological changes
  * Platform stability
  * Hand movements/dexterity
  * Crew Medical Officer (CMO) training
  * Bleeding
  * Post-LP headache
Risk of Infection

- Infection considered the most likely in-flight complication according to the VIIP Advisory Panel

- Sterile technique used to conduct LPs terrestrially

- Potential challenges:
  - Microscopic floating debris contaminating the sterile field
  - Bacterial counts and growth rates, bacterial virulence, and antibiotic resistance appear to be higher in space flight
  - Immune system dysregulation may play a role in increasing susceptibility

- Potential mitigations:
  - Performance of the in-flight procedure close to planned day of deorbit so astronaut is back on Earth by the time potential infectious complications would be expected to manifest
  - Optimizing hand sanitation and adding additional layers of sterility
Approach to Increasing LP Data

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Challenges - Ethics

→ Aspects to consider include:
  - Mandatory vs. voluntary
  - VIIP Advisory Panel repeatedly recommended that NASA consider mandating pre- and postflight LPs for all crewmembers as part of medical requirements
  - Formal evaluation by a NASA HQ appointed bio-ethicist concluded that LPs cannot be mandated in the absence of clinical indications, but they can be conducted on a voluntary basis as part of research

→ Development of an LP study under the VIIP research plan
  - Pre- and postflight testing
  - Optional in-flight module if safety and logistical challenges can be overcome
Approach to Increasing LP Data

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Logistics

Implementation
Challenges – Logistics

Logistical aspects to consider:

- Optimal timing of LP
- CSF parameters to be tested
- Use of restraints in-flight
- Ultrasound guidance
- Optimal equipment (numerous types of needles)
- Consistency in data collection and equipment
- Location
Challenges – Logistics

→ Optimal timing of procedure
  ♦ Preflight - Several months prior to mission, to allow resolution of any (most likely minor) complications
  
  ♦ In-flight – Several options discussed with VIIP Advisory Panel:
    ~ Soon after launch since ICP would be at its highest
    ~ After 3 months, when a physiological steady-state has been reached
    ~ Prior to landing, in case of complications
  
  ♦ Postflight – Several days after landing (R+3)
    ~ Recover from microgravity-induced neurovestibular dysfunction
    ~ After the R+3 MRI (rule out contraindications)
    ~ Minimize interference with data collection for other postflight tests

→ CSF parameters to be tested
  ♦ >20 parameters are possible in addition to standard ones
    ~ Limited literature, limited shelf life of collected CSF, limit in how much CSF can be collected for evaluation
Approach to Increasing LP Data

- **Safety**: Risk analysis for pre/postflight and in-flight
- **Ethics**: Mandatory vs. voluntary
- **Logistics**: Implementation
Challenges - Implementation

Aspects to consider include:

- Space Medicine Operations buy-in
- Institutional Review Board (IRB) approval
- Recruiting crewmembers
Conclusions and Path Forward

- Benefits of ascertaining ICP include the ability to develop targeted countermeasures and treatment options.

- Potential risks are small for pre/postflight LP, more uncertainty for in-flight LPs.

- Risk for in-flight LP may be minimized by establishing training, techniques, hardware and procedures for such an endeavor, and validating those in parabolic flights.

- LP limitations - Provides a one-time pressure measurement, whereas ICP is dynamic and varies diurnally as well as with activity and posture.

- Efforts to develop non-invasive ICP technologies will continue, alongside evaluations of novel minimally-invasive technologies.
Thank You

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