# **Protocol for “****Emerging Therapies in Intracranial Pressure Management: Targeting the Systemic Venous System” Nicolas H. Norager, Casper S. Riedel, Alexander Lilja-Cyron, Tina N. Munch and Marianne Juhler**

**Keywords:** Intracranial pressure, cerebral perfusion pressure, central venous pressure, systemic venous system, venous outflow regulation, , neurocritical care

**Research question**

What systemic venous-targeted intracranial pressure interventions can be identified in the literature, and what is their effectiveness in managing intracranial pressure (ICP) and improving cerebral perfusion pressure (CPP)?  
  
**Background**  
Elevated ICP remains a major challenge in neurocritical care, contributing significantly to morbidity and mortality.1–3 Traditional management strategies have largely focused on cerebrospinal fluid (CSF) regulation and arterial blood flow, with less emphasis on the venous system despite its substantial influence on intracranial dynamics.4,5 The Monro-Kellie doctrine describes the brain, blood, and CSF as a closed system in which any volumetric change in one component must be compensated by another or the pressure will increase rapidly.6 While CSF production and removal are relatively slow processes, cerebral blood flow is highly dynamic, with venous outflow playing an important role in ICP regulation.7–9  
  
Despite its physiological significance, venous outflow has been historically overlooked as a therapeutic target for ICP management.4 The volume of intracranial venous blood is comparable to that of CSF, and even minor alterations in venous drainage can therefore likely lead to significant changes in ICP in patient on the far right of the pressure-volume curve.5 Impaired venous outflow due to increased central venous pressure, thoracic or abdominal hypertension, or local venous obstruction has been implicated in various conditions associated with intracranial hypertension.4,9–11 Current strategies for managing venous-related ICP elevations remain largely conservative, including interventions such as optimizing head positioning, avoiding cervical collar and external compression of the jugular veins.2  
  
Emerging interventions, including mechanical and pharmacological strategies, may offer new avenues for modulating venous drainage and improving ICP regulation.11–14 This systematic review aims to identify and evaluate the current evidence on systemic venous-targeted intracranial pressure interventions, providing insights into their effectiveness and potential role in ICP management.

### **Methods**

**Eligibility criteria**  
**PICO**   
**Population (P):**  
Patients with elevated intracranial pressure due to any etiology receiving systemic venous-targeted ICP intervention.  
  
**Intervention (I):**  
Venous-targeted strategies, including but not limited to:  
 - Impedance Threshold Device

### Lower Body Negative Pressure (LBNP)

### Intrathoracic Pressure Regulation (ITPR)

### Nitroglycerin

### Thigh Cuffs

### **Comparator (C):** In this review, we focus on the effectiveness of the interventions in reducing ICP, and therefore there will not be a comparator.

### **Outcomes (O):** Reduction in ICP. Increase in CPP. Adverse events

**Eligibility of studies**

Studies will be excluded if they do not meet the following criteria:

1. Studies must provide direct or indirect measurements of either ICP or CSF opening pressure.
2. Only studies conducted in humans will be included; thus, studies based on animal models will be excluded.
3. Studies must include interventions specifically targeting the systemic venous system for ICP management.
4. Studies must be published in English and undergo peer review.
5. Studies focusing on patients treated for specific intracranial venous pathologies or obstructions using well-established methods (e.g., surgical shunts, stents or thrombectomy) will be excluded.

A total of four reviewers will independently assess the eligibility of studies through a two-stage screening process. Each article will be independently evaluated by two assigned reviewers.

In the first stage, titles and abstracts will be independently screened by two reviewers to determine inclusion based on predefined eligibility criteria. Studies deemed irrelevant will be excluded, while those meeting the inclusion criteria or requiring further assessment will proceed to full-text review. Any disagreements at this stage will be discussed between the two assigned reviewers, and if consensus cannot be reached, a impartial expert reviewer (TNM) will make the final decision.

In the second stage, full-text versions of potentially relevant studies will be retrieved and independently reviewed by the same two reviewers, applying the inclusion criteria. Any discrepancies in study selection at this stage will be resolved through discussion, with arbitration by the impartial expert reviewer (TNM)

The screening and data extraction process will be conducted using systematic review software such as Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). If necessary and feasible, corresponding authors of included studies will be contacted to obtain additional information relevant for the reviewers' assessment. Reviewers will not be blinded to study authorship or institutional affiliation.

### **Databases** A systematic search will be conducted in the following databases:

* **MEDLINE Ovid** (1946 to present)
* **Embase Ovid** (1974 to present)
* **Conference Proceedings Citation Index – Science (Web of Science)** (1990 to present)

### **Search Strategy** The search will include terms related to intracranial pressure, venous drainage, and interventions. The searches will include no restrictions on the publication period or study design. If relevant studies lack sufficient published data, the corresponding authors will be contacted to retrieve additional information. The detailed search strategies for each database are provided in Appendix 1.

To supplement the database search, reference lists of included studies will be manually screened for additional relevant literature. Experts (TNM) in the field will also be consulted to identify any potentially missing studies.

**Data Collection**  
The following data will be extracted:  
  
Study design and characteristics including:  
- Study type (e.g., RCT, observational, case report).  
- Description of the study design.  
- Primary and secondary aims.  
- Sample size, study setting, and funding source.

Demographic data including:  
- Age and gender.  
- Comorbidities and underlying cause of elevated ICP.  
- Weight and body mass index (BMI).

Intervention details including:

- Type of intervention (e.g., device, pharmacological, mechanical).

- Dosages or magnitude of intervention (e.g., pressure changes, drug doses).

- Duration and frequency of the intervention.

- Baseline measurements, including ICP, MAP, CPP, heart rate, and oxygen saturation.

- Use of other ICP-lowering measures alongside the intervention being studied.

Outcomes including:

- Effect on ICP and intracranial pulse wave amplitude.

- Impact on MAP, CPP, pulse, and other measures of intracranial compliance or cerebral blood flow.

#### Adverse events including - Complications and adverse events related to the intervention. - Severity and classification of these events.

If published data was insufficient, the authors were contracted to retrieve raw data.

**Quality assessment**   
The validity and methodological quality of all trials will be evaluated. A priori, we do not expect many, if any, randomized clinical trials on this topic due to the emerging natur og venous-targeted intervention. Therefore, we use a quality assessment method relevant for observational studies. We will use Newcastle-Ottawa Scale (NOS). The methodological quality of the study will be independently assessed by two investigators.

**Data presentation**

**Flow chart**A PRISMA flowchart will be used to illustrate the study selection process. The flow diagram will outline the total number of studies identified through the search, the number of duplicates removed, the number of studies screened at the title and abstract level, the number of full-text articles reviewed, and the final number of studies included in the analysis.

**Study characteristics**  
The characteristics of participants for each treatment will be summarized in tables which provides the following information: number of participants, age, sex, weight/BMI, comorbidities, and the type of intervention applied.

**Methodological quality**  
As outlined previously, the methodological quality of included studies will be assessed using the Newcastle-Ottawa Scale (NOS). An average NOS score will be calculated and reported for each treatment modality.  
  
**Statistical analysis**  
Given the anticipated limited number of randomized controlled trials, a meta-analysis is unlikely to be feasible. Instead, data will be presented narratively, emphasizing descriptive statistics and trends across studies.

For each intervention, data will be pooled and analyzed collectively. Raw data will be assessed for normality, and where normally distributed, results will be presented as mean ± standard deviation along with 95% confidence intervals. If appropriate, parametric tests such as Student’s t-test will be used to assess the effect of interventions on ICP, CPP, and MAP. For non-normally distributed data, appropriate non-parametric tests will be applied.

All statistical analyses will be conducted using a relevant statistical software program, such as RStudio.

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