Effectiveness of intrathecal nicardipine on cerebral vasospasm in non-traumatic subarachnoid hemorrhage: a systematic review protocol

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Review question/objective: The objective of this review is to determine the effectiveness of intrathecal (IT) nicardipine on cerebral vasospasm and its impact on the following outcome measures: mean flow velocities, angiographic and/or clinical vasospasm and infection rates. Specifically, the review question is: What is the effectiveness of IT nicardipine on cerebral vasospasm in adult patients with aneurysmal subarachnoid hemorrhage?

Keywords Cerebral vasospasm; intrathecal nicardipine; non-traumatic subarachnoid hemorrhage

Background

Worldwide, nine out of 100,000 people will suffer from subarachnoid hemorrhage (SAH) annually; numbers vary according to region.1 Annually, a total of 30,000 people will suffer from SAH in the United States.1 Japan and Finland have the highest annual SAH occurrences affecting 22.7 out of 100,000 people and 19.7 out of 100,000 people, respectively, while Central and South America’s annual occurrence of SAH averages 4.2 out of 100,000 people.1 China’s annual occurrence of SAH has been reported as low as 2.0 out of 100,000 people.1 Based on a study conducted in 2004, there are 500,000 deaths worldwide and the combined annual cost for those who suffered aneurismal subarachnoid hemorrhage (aSAH) and the ones caring for them was an estimated $138,000,000.2 Subarachnoid hemorrhage occurs when blood has spilled into the space between the arachnoid and pia matter. The majority of non-traumatic SAH occurs as a result of ruptured aneurysms and arteriovenous malformation. Cerebral aneurysms have a tendency to form where cerebral arteries bend and branch off one another. Hemodynamic stress, along with weakened areas within the arterial wall, further increases the risk of aneurysm development; larger aneurysms have a higher tendency to rupture. Once an aneurysm rupture occurs, blood enters into the subarachnoid space and is spread throughout the cerebral spinal fluid (CSF) space. Once blood enters the CSF space, the patient is at risk for a host of complications including meningeal irritation, elevations in intra-cranial pressure (ICP), hydrocephalus and cerebral vasospasm.3 Risk factors for SAH include, but are not limited to, smoking, heavy alcohol consumption, hypertension and hormone replacement therapy; women tend to have higher occurrences reported.3 There are many complications that are associated with aSAH; however, delayed cerebral ischemia resulting from vasospasm is considered to be the most detrimental in terms of mortality and morbidity.3 Cerebral ischemia secondary to cerebral vasospasm is the major concern due to its irreversible effects on brain tissue. Delayed ischemic neurological deficit (DIND) as a result of aSAH is the number one reason for death and disability.4 There is a direct correlation between the amount of subarachnoid blood and the degree of cerebral vasospasm.5 Cerebral vasospasm after SAH can be defined in two ways: angiographic vasospasm and clinical vasospasm. Angiographic cerebral vasospasm is witnessed with radiographic imaging and becomes evident typically four days after SAH and peaks around day seven. Clinical vasospasm after SAH becomes evident when there is a change in
clinical status such as altered level of consciousness, motor deficits and/or sensory deficits. Clinical signs can worsen when blood pressure drops due to a decline in cerebral perfusion.\(^5\) The onset of cerebral vasospasm can be delayed up to 21 days post-aneurysmal rupture.\(^2\) Seventy per cent of those who suffer SAH will have angiographic cerebral vasospasm; 40% of those who experience cerebral vasospasm will suffer clinically. Thirty per cent will witness a delayed ischemic injury and up to 20% of patients will suffer from severe deficits, or even worse, die as a result of the effects of cerebral vasospasm.\(^5\)

Vasospasm is a multi-factorial process that is not completely understood; however, the cascade of events that lead to spasm has led to much research on effective ways of managing cerebral vasospasm.\(^7\) The use of transcranial Doppler (TCD) ultrasonography is a widely accepted and proven means of predicting vasospasm through measurement and trending cerebral mean flow velocities (MFVs). Vasospasm is present when MFVs reach 120 or greater; although the clinical signs may not be present, treating the patient based on MFVs obtained from TCD measurements can be useful in preventing clinical vasospasm.\(^8\) The Lindegaard ratio is used to diagnose vasospasm based on calculated TCD measurements using MFVs obtained from the middle cerebral artery (MCA) and the ipsilateral internal carotid artery (ICA). Mild-to-moderate vasospasm is defined as an MCA velocity 3–6 times higher than the ICA velocity and greater than six would indicate severe vasospasm.\(^9\)

Currently, there are several accepted ways of managing cerebral vasospasm including, but not limited to, optimizing cardiac output with the use of inotropes, oral nimodipine, endovascular intraarterial (IA) vasodilation, endovascular balloon angioplasty, intravenous (IV) calcium channel agents, intrathecal (IT) therapies (nimodipine and fibrinolysis), Triple-H therapy (Hypervolemia, Hemodilution and Hypertension), statin therapy, magnesium sulfate infusions and through the use of mechanical means such as lumbar drain placement.\(^10\) Surgically placed nimodipine prolonged release implants have also proven to prevent vasospasm.\(^11\) Although many modalities exist, oral nimodipine and Triple-H therapy, specifically hypertension, are the most supported means of treatment. Oral nimodipine is the only therapy to consistently improve outcomes following aSAH.\(^5\)

Studies have proven that although the use of oral nimodipine reduces cerebral infarction in aSAH by 34% and the rate of poor outcomes by 40%, its use does not have any significant effect on cerebral vasospasm.\(^7\) Nicardipine, like nimodipine, is a calcium channel antagonist that prevents the influx of extracellular calcium leading to a reduction in smooth muscle contraction, therefore preventing vasoconstriction. Nicardipine can be administered intravenously, locally through IA and IT routes. Studies demonstrate the efficacy of IV nicardipine in the reduction of cerebral vasospasm; however, there are associated risks including hypotension leading to a decline in cerebral perfusion pressure, pulmonary edema and azotemia.\(^12\) Studies have proven that the use of IT nicardipine is not only effective in the reduction and prevention of cerebral vasospasm, but also safe. Shibuya et al.\(^13\) conducted a study on 141 patients, 50 of whom received IT nicardipine and the remaining were placed in the control group. Of the 50 who received IT nicardipine, the incidence of clinical vasospasm was reduced by 26% and angiographic vasospasm was reduced by 20%; clinical outcomes were improved by 15%. Although effective in the treatment of cerebral vasospasm, there were nine reported cases of headache and two reported cases of meningitis.\(^13\) Suzuki et al.\(^14\) conducted a study on the use of IT nicardipine on 177 patients who presented with a Hunt and Hess Scale of 1–3 (minimal neurological deficits such as drowsiness) and a computed tomography (CT) scan demonstrating a Fisher Grade III (localized clots or vertical layers of blood 1 mm or more thickness). The study revealed that out of 177 patients, 20 patients demonstrated angiographic vasospasm, while only ten demonstrated clinical vasospasm. Improved outcomes were exhibited in 89.2% of those in the study, which was defined as no worse than moderate disability six months following the initial hemorrhage.\(^14\) Although safety and efficacy have been demonstrated with the IT administration of nicardipine, the risk of central nervous system (CNS) infection does exist when directly accessing the CSF space for IT therapy. A small percentage (6.2%) of the 177 patients in the study conducted by Suzuki et al.\(^14\) did acquire a CNS infection with IT nicardipine administration.

By understanding the concept of cerebral vasospasm and the defining attributes associated with it, one understands the risk and detrimental effects of
cerebral ischemia as outlined above. Outcomes only worsen as the severity of cerebral vasospasm increases.\textsuperscript{15} Due to the devastating effects and outcomes associated with cerebral vasospasm and DIND, more treatment modalities are needed. Currently, nimodipine is the only Food and Drug Administration-approved medication for treating and improving outcomes in the setting of aSAH. An advantage of IT nicardipine is that it can be given locally through an already existing external ventricular drain (EVD), a CSF flow diversion device also used to measure ICP, making this route not only appealing, but effective in terms of proven reduction in MFVs as evidenced through the use of TCDs.\textsuperscript{16} Intrathecal nicardipine has proven to be both effective and safe for treating cerebral vasospasm in aSAH.

Databases were searched for guideline recommendations on the use of IT nicardipine in aSAH. DynaMed and UpToDate yielded no results on recommendations for IT administration; however, Micromedex recommended either 2-mg IT every 8 h or 4 mg every 12 h based on studies conducted by Shibuya et al.\textsuperscript{13} and Suzuki et al.\textsuperscript{14} respectively. An extensive search for existing systematic reviews examining the use of IT nicardipine in the management of cerebral vasospasm was conducted, and none were found. The databases searched included Campbell Systematic Reviews, Cochrane, DARE, PROSPERO and JBI Database of Systematic Reviews and Implementation Reports. The search was conducted in January 2016.

**Inclusion criteria**

**Types of participants**

The current review will consider studies that include:

- Adults (18 years and older)
- Intensive care
- Non-traumatic SAH – diagnosed by CT head and without history of trauma as cause of SAH.
- Presence of EVD.

Exclusion criteria:

- Traumatic SAH – that have occurred as a result of trauma (i.e. head trauma from motor vehicle crash, gunshot wound, falls, etc.).
- Participants who are 17 years of age or under.

**Types of intervention(s)**

The current review will consider studies that evaluate the use of IT nicardipine on cerebral vasospasm in the setting of non-traumatic SAH compared to those not receiving IT nicardipine. Micromedex recommends two dosing options: 2 mg every 8 h or 4 mg every 12 h. Both dosing options will be considered in this review. Neither administration of any and/or other medications nor recognized confounding factors will lead to exclusion from this review.

**Outcomes**

The current review will consider studies that include the following primary outcome measures: MFVs measured by TCD and the presence of angiographic and/or clinical vasospasm. Secondly, infection rates as a result of IT nicardipine administration will be evaluated. Although onset and peak vasospasm periods occur mainly within a two-week period following aneurysmal rupture, cerebral vasospasm can be delayed up to three weeks. For this reason, interventions and results will be evaluated for a three-week period following aneurysmal rupture.

**Types of studies**

The current review will consider both experimental and epidemiological study designs including randomized controlled trials, non-randomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies and case-control studies.

**Search strategy**

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Third, the reference list of all retrieved reports and articles will be searched for additional studies. Studies published in English will be considered for inclusion in this review. Date limitations on published studies will not be used during the literature search for this review. The databases to be searched include: Cochrane CENTRAL, DynaMed, Embase, PubMed.
Micromedex
UpToDate
The search for unpublished studies will include:
MedNar
Initial keywords to be used will be
Subarachnoid hemorrhage
Vasospasm
Nicardipine
Intra-ventricular
Intrathecal

Assessment of methodological quality
Studies that may meet the inclusion criteria will be retrieved in full and their details imported into the Joanna Briggs Institute’s System for the Unified Management, Assessment and Review of Information (JBI-SUMARI). The full text of selected citations will be retrieved and assessed in detail against the inclusion criteria by two independent reviewers. Full-text studies that do not meet the inclusion criteria will be excluded, and reasons for exclusion will be provided in an appendix in the final systematic review report. Selected studies will be critically appraised by two independent reviewers at the study level for methodological quality in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I).

The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. The results of critical appraisal will be reported in narrative form and in a table.

Data extraction
Data will be extracted from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II) by two independent reviewers. All data will be subject to double data entry. The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data where required.

Data synthesis
Papers will, where possible, be pooled in statistical meta-analysis using JBI-SUMARI. Effect sizes will be expressed as either odds ratios (for dichotomous data) and weighted (or standardized) mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-squared and $I^2$ tests. Subgroup analyses may be explored based on different study designs included in this review. Sensitivity analyses will be conducted to test decisions made regarding the effects of IT nicardipine on cerebral vasospasm. Where statistical pooling is not possible, the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

References


Appendix I: MAStARI appraisal instrument

**JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial**

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<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
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<td>1. Was the assignment to treatment groups truly random?</td>
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<td>2. Were participants blinded to treatment allocation?</td>
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<td>3. Was allocation to treatment groups concealed from the allocator?</td>
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<td>4. Were the outcomes of people who withdrew described and included in the analysis?</td>
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<td>5. Were those assessing outcomes blind to the treatment allocation?</td>
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<td>6. Were the control and treatment groups comparable at entry?</td>
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<td>7. Were groups treated identically other than for the named interventions</td>
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<td>8. Were outcomes measured in the same way for all groups?</td>
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<td>9. Were outcomes measured in a reliable way?</td>
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<td>10. Was appropriate statistical analysis used?</td>
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Overall appraisal: Include □ Exclude □ Seek further info. □

Comments (including reason for exclusion)

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### JBI Critical Appraisal Checklist for Descriptive / Case Series

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<td>1. Was study based on a random or pseudo-random sample?</td>
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<td>3. Were confounding factors identified and strategies to deal with them stated?</td>
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<td>4. Were outcomes assessed using objective criteria?</td>
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<td>5. If comparisons are being made, was there sufficient descriptions of the groups?</td>
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<td>6. Was follow up carried out over a sufficient time period?</td>
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<td>7. Were the outcomes of people who withdrew described and included in the analysis?</td>
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- Seek further info [ ]

Comments (Including reason for exclusion)

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# JBI Critical Appraisal Checklist for Comparable Cohort/Case Control

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<td>1. Is sample representative of patients in the population as a whole?</td>
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<td>2. Are the patients at a similar point in the course of their condition/illness?</td>
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<td>3. Has bias been minimised in relation to selection of cases and controls?</td>
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<td>4. Are confounding factors identified and strategies to deal with them stated?</td>
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**Overall appraisal:** Include ☐ Exclude ☐ Seek further info. ☐

**Comments (Including reason for exclusion):**

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Appendix II: MASTARI data extraction instrument

**JBI Data Extraction Form for Experimental / Observational Studies**

- **Reviewer** 
- **Date**
- **Author** 
- **Year**
- **Journal** 
- **Record Number**

**Study Method**

- RCT
- Quasi-RCT
- Longitudinal
- Retrospective
- Observational
- Other

**Participants**

- **Setting**
- **Population**

**Sample size**

- **Group A**
- **Group B**

**Interventions**

- **Intervention A**
- **Intervention B**

**Authors Conclusions:**

- 
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- 

**Reviewers Conclusions:**

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## Study results

### Dichotomous data

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### Continuous data

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