Defining Optimal Dosing of Nimodipine in Aneurysmal Subarachnoid Hemorrhage: Study Protocol for a Systematic Review

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Abstract

Background: Nimodipine has been first line prophylaxis of cerebral vasospasm after subarachnoid hemorrhage for more than three decades, but its level of evidence has become controversial and essential questions regarding its pharmacological properties and its precise mechanism of action remain unclear. The level of evidence for Nimodipine was established in times when subarachnoid hemorrhage patients had their aneurysm secured in a delayed phase and when intravascular coiling was not established, these two clinical scenarios differ from current practice questioning the applicability of its therapeutic regimen. This review aims to investigate the strength of nimodipine as a prophylaxis for cerebral vasospasm within a contemporary context and to propose pathways for future research in nimodipine.

Methods: We will search electronic databases including Medline, Embase, Cochrane, Web of Science and PubMed using a defined search strategy. Two authors will independently rate the quality of the searched evidence using the Chalmers scale for the scoring of studies 'quality. Discrepancies will be assessed by a third independent author. All studies will be described in a table of studies' characteristics and data extraction completed. Meta-analysis will be performed if there are two or greater homogeneous outcomes that suffices for reporting on measures of variability.

Discussion: The results rising from this systematic review may guide further clinical trials focused on nimodipine dosing with the view of optimizing therapy for better neurological outcomes.

Systematic review registration: PROSPERO ID = CRD42020188319

Background

The incidence of aneurysmal subarachnoid hemorrhage (SAH) demonstrates considerable geographical and seasonal variability [1] and is one of the leading causes of morbidity and mortality within industrialized societies [2]. Patients frequently require acute management in intensive care units (ICU) prolong hospital and rehabilitation stays with associated high impact on health economics [3, 4]. Further-more, SAH has a considerable impact on functional, psychological and social integration to community [5, 6]. Over the past two decades there have been sophisticated advances in neuroradiology and neuro-interventional rescue strategies [7–9]; however cerebral vasospasm continues to be a common complication which may lead to cerebral infarct and irreversible effects on neurological outcome. Within this scenario of evolving advances, nimodipine remains the main prophylaxis to cerebral vasospasm, however its role and mechanism of action is controversial [10–13]. Multiple factors may contribute to poor neurological outcomes. Suboptimal levels of nimodipine at the Pial arteries and the subarachnoid space, where vasospasm initiates may be a trigger for vasospasm [14]. Although the evidence for nimodipine was based on studies that used a weight-adjusted dose [15], fixed dosing regimens became standard of practice [16]. Given the wide potential variability in absorption and dose-effects related to individual variability, it is possible that current fixed dose prescriptions may be suboptimal. Therapeutic dose monitoring strategies (TDM) could optimize nimodipine dosing in these patients. In addition to vasospasm, other processes such as cerebral arterial micro-thrombosis [17], cerebral autoregulation dysfunction, collateral flow dynamics [18] and cortical spread depolarization [19] have shown to contribute to cerebral infarct, independently of vasospasm.

The objective of this study is to conduct a systematic review of the published literature in order to appraise the evidence between nimodipine prophylaxis and neurological outcome related to cerebral vasospasm with an emphasis on examining the dose-effect relationship.

Review Questions

1. Does nimodipine reduce the incidence of cerebral vasospasm related neurological deficits?
2. Does nimodipine reduce the incidence of cerebral infarct related to cerebral vasospasm?
3. How does the current nimodipine prescription (fixed-dose) correlate with neurological outcomes when compared to an individualized (weight-based) dose?

Methods / Design

Protocol and study overview

This systematic review will comply with the requirements' checklist and recommendations described by the PRISMA Statement [20]. We will conduct an extensive literature search from the wider topic of subarachnoid hemorrhage to the narrower search of the dose response of nimodipine using additional filters and advanced searches. Our intention is to achieve the most specific but also thorough database to ensure that all relevant studies, are included. Because this is a very focused topic with a-priori expectations of few randomized trials, we will include pharmaco-kinetic studies and non-randomized studies to avoid missed information. This protocol will be registered at the PROSPERO international prospective register of systematic reviews.

Selection Criteria

Population

The sample of interest will include: adults admitted to a tertiary ICU with the diagnosis of aneurysmal SAH of any grade; defined by: the presence of subarachnoid blood in the subarachnoid space with or without a demonstrated aneurysm on cerebral computerized tomography (CT) angiography or patients with a normal CT but a positive xanthochromia index on the lumbar puncture (LP) and with or without demonstrated aneurysm; patients with peri-mesencephalic SAH will also be included.

Types of outcome measure

Primary outcome measure:

- Clinical outcome benefit, defined as a reduction in neurological deficits only related to cerebral vasospasm.

Secondary outcome measures:

- Clinical outcome benefit, defined as a reduction on the incidence of cerebral infarcts, diagnosed via CT Scanner and attributed and / or confirmed to cerebral vasospasm.

Tertiary outcome measures:

- Clinical outcome benefit, defined as a reduction on neurological sequela including cerebral infarcts of all causes between two different nimodipine prescription regimens (a fixed and a weight-based regimen).

Search strategy

The search will comprise four stages

1. A limited search of Medline to identify relevant keywords
2. Identified terms and the synonyms will be used to conduct an extensive search of the literature
3. Reference lists will be collected from included articles and key author searches will be conducted.
4. The initial search will be undertaken by two investigators (JP and JB). Additional input from a senior librarian will enable the search to have maximal robustness. Three database searches with superimposed filters and criteria will be combined and duplicates will be removed. Four databases will be interrogated: Pubmed, EMBASE, Web of Science and Cochrane, through the library tools of the University of Queensland.

The search will cover the following terms: “subarachnoid hemorrhage”, “subarachnoid haemorrhage”, “nimodipine” or “calcium channel blockers”, “dose response” or “dose response relationship” including Medical Subject Headings (MeSH) terms. Finally a combination of these terms-search will be implemented using the Boolean operators of: “AND” (to combine “subarachnoid hemorrhage/ haemorrhage” with “nimodipine”), “OR” (when referring to “nimodipine” OR “Calcium Channel Blockers” as well as “dose response” OR “Dose response relationship”) “AND” (to combine ”Subarachnoid hemorrhage/haemorrhage” with “nimodipine” or “Calcium channel blockers” and with “dose response” or “dose response relationship”).

Selection process

Two investigators (JP and JB) will independently screen the selected abstracts to identify studies that focus on: dosing of nimodipine in SAH; pharmaco-kinetic and pharmaco-dynamic (PK/PD) data; pathway of administration (enteral or parenteral); radiological and clinical response to nimodipine; presence of a “neuro-worsening” defined as a drop in two points on the Glasgow Coma Score (GCS) or the presence of a new neurological deficit; neurological outcomes secondary to cerebral vasospasm such as delayed ischemic neurological deficit (DNID), cerebral infarct and death.

Types of Studies

- We will include prospective cohort studies, randomized controlled trials (RCT), systematic reviews and metanalyses if possible. We will include studies published from January 1, 1980 to current date and publications written in English and Spanish.
- We will exclude retrospective cohort and didactic (editorial) studies; experimental or animal models; publications prior to the inclusive date; studies only focusing on radiological response to nimodipine (specifically when used intraarterially for the treatment of established vasospasm); studies that are based on general management of SAH as opposed to focused dose-effect of nimodipine; trials using historical controls; dose-finding studies not including a placebo-control group.

Study records- data collection process

The two investigators (JP and JB) will independently read all selected studies and complete a scoring sheet that will have been previously designed for the purpose of extracting data homogeneously across all studies (Table 1). The data extracted will be based on this systematic review’ s endpoints and disclosed in three tables:

Table 1: Studies scoring criteria (Chalmers scale)

Authors	SDRL	RSG	AC	Blinded Patients	Placebo	Blinded Personnel	ENES	ASA	COD	CNSR
SUMMARY (Overall percentage)										

SDRL: Selection Description and Reject Log; RSG: Random Sequence Generation; AC: Allocation Concealment; Blinded Patients: blinding of Subarachnoid hemorrhage patients; Placebo: Use of placebo in controls; Blinded Personnel: Blinding of nurses and physicians; ENES: Estimation of numbers, endpoints, significance; Asa: Appropriate Statistical Analysis; COD: Complete Outcome Data: CNSR: Complete Non-Selective Reporting.

- Publication details: year and language of publication; country were studies were performed for each selected study.
- Design of studies: Type of study, patient enrollment (consecutive or non-consecutive).
- Primary outcome data: presence of confirmed cerebral vasospasm and secondary neurological deficit's severity (Table 2).
- Secondary outcome data: presence of cerebral vasospasm and secondary cerebral infarction, or infarction of all causes (Table 3).
- Neurological deficits of all causes amongst groups with different nimodipine prescription-regimen (fixed-dose compared to weight-based dose) in Table 4.

Table 2: Cerebral vasospasm related neurological deficit amongst groups (primary endpoint)

Author	Drug	Drug	Drug	Drug	Drug	Placebo	Placebo	Placebo	Placebo	Place
Year	No vasospasm	No vasospasm	vasospasm	**vasospasm**	**vasospasm**	No vasospasm	No vasospasm	vasospasm	**vasospasm**	**vaso**
	No neurological deficit	with neurological deficit	No neurological deficit	**with neurological deficit**	**with Death**	No neurological deficit	with neurological deficit	No neurological deficit	**with neurological deficit**	**with Deat**

Table 3: Cerebral infarction of all causes amongst groups (secondary endpoint).

Author	Drug No vasospasm No Cerebral infarction	Drug No vasospasm with Cerebral infarction	Drug vasospasm No Cerebral infarction	**Drug** **vasospasm** **with Cerebral infarction**	**Drug** **Infarct of all causes**	Placebo No vasospasm No Cerebral infarction	Placebo No vasospasm with Cerebral infarction	Placebo vasospasm No Cerebral infarction	**Placebo** **vasospasm** **with** **Cerebral** **infarction**	**Placebo** **Infarct of all causes**

Table 4: Neurological deficits, infarcts and death between fixed-dose regimen of nimodipine and weight-based regimen.

Authors	Drug Neurological deficit	Drug Cerebral Infarcts	Drug Death	Placebo Neurological deficit	Placebo Cerebral Infarct	Placebo deaths
Fixed dose regimen						
Weight-based regimen						

Quality assessment and risk of bias in individual studies:

The two investigators (JP and JB) will independently assess the risk for bias within the selected studies. Only those selected studies for which both investigators agree in the accomplishment of all selection criteria will be included in the final systematic review.

Data Synthesis

Descriptive narrative of the data will be combined with a quantitative meta-analysis, when possible. Studies will be grouped by study design (randomized); location (single or multicenter); outcome measures; description of nimodipine dose; definition and inclusion of cerebral vasospasm. Following studies' grouping, these characteristics will be presented in summary tables.

Statistical Analyses

Data extraction will be completed for all included studies. To compare results between trials, for continuous outcomes an unbiased effect size estimator with 95% confidence intervals will be calculated, (Comprehensive Meta-Analysis™ software, version 2 (Biostat, Englewood, NJ, USA). Dichotomous outcomes will be expressed as risk ratios with 95% confidence intervals.

Where possible, we will use a random-effects meta-analysis with the inverse variance method to estimate the pooled crude effect estimates [21]. To assess heterogeneity between studies, the I^2 statistics will be calculated. If quantitative synthesis is not appropriate, observational studies will be reported in a descriptive tabular fashion.

Publication bias at the outcome level will be investigated by displaying relationships between study sizes and effect sizes in funnel plots, using Stata™ software version 14.0 (StataCorp, College Station, TX, USA). The quality of each selected RCT will be appraised using the Chalmers scale [22]. For the dose-

response vs neurological outcomes analysis we studied specific slopes (linear trends) and 95% confidence intervals from the natural logs of the relative risks and confidence intervals across categories of doses of Nimodipine.

An overview of the search, screening, selection and scoring process is shown in the flowchart below, according to PRISMA requirements [20]:

Discussion

This systematic review and meta-analysis will examine the published data regarding the prophylactic benefits of nimodipine on neurological deficits and cerebral infarction as a complication of cerebral vasospasm in patients with subarachnoid hemorrhage. It will also assess the potential impact of dosing of nimodipine by analyzing neurological outcome in two cohorts: patients who received a fixed-dose of nimodipine versus patients who received a weight-based regimen of nimodipine. The authors will classify the selected RCTs according to two main aspects of their methodology: confirmation of cerebral vasospasm as a cause for neurological deficits including cerebral infarct and death versus RCTs that report neurological outcomes of all causes without the confirmation of cerebral vasospasm.

The authors' main justification for conducting this systematic review is that current evidence of nimodipine is based upon studies that do not reflect contemporaneous clinical scenarios. The authors of this systematic review hypothesize that current prescription practices on nimodipine lack sufficient evidence and that a specific cohort of patients who may benefit the prophylactic use of nimodipine is yet to be described. In addition, we hypothesize that the potential benefit for nimodipine may be dependent upon an individualized dosing regimen as opposed to current prescription practices. The results of this systematic review are expected to be available at the end of 2020.

Abbreviations

SAH
Subarachnoid Hemorrhage; ICU:Intensive Care Unit; TDM:Therapeutic Drug Monitoring; CT:computerized Tomography; LP:lumbar Puncture; PK/PD:Pharmacokinetic / pharmacodynamic; GCS:Glasgow Coma Scale; DIND:Delayed Ischemic Neurological Deficit; CSF:Cerebro Spinal Fluid; RCT:Randomized Control Trial.

Declarations

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Authors' contributions

JB established the topic of review, implemented the database search, independently selected and scored the searched studies and wrote the manuscript drafts. K.B. L reviewed the protocol manuscript and supported with expert advice; Jeff Lipman added expert advice and contributed to the editing of the manuscript; Jason Roberts offered expert advice and contributed to the editing of the manuscript; Eva Malacova conducted the statistical analysis and contributed with expert advice; JP performed the database search, independently selected and scored the searched studies, reviewed the manuscript drafts and supported with expert advice.

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Consent for publication: Not applicable

Competing Interests: The authors declare that they have no competing interests.

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