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Original Article

Nimodipine administration routes' role on Aneurysmal Subarachnoid Hemorrhage outcomes - A retrospective cohort study

A via de administração de nimodipino em desfechos da Hemorragia Subaracnóidea Aneurismática - Uma coorte retrospectiva

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ABSTRACT

Aim of the study: To evaluate the role Nimodipine administration route (oral or feeding tube) in the outcome of vasospasm (at 7 and 21 days) in patients hospitalized with aneurysmal subarachnoid hemorrhage (SAH). **Methods**: The study has a retrospective cohort design, with data collected in a tertiary teaching hospital in Porto Alegre, Brazil. The period analyzed was between January 2019 and January 2023. Patients over 18 years old, diagnosed with SAH and who underwent at least 7 days of hospitalized nimodipine treatment were included. **Results:** A total of 121 patients were included: 59 received nimodipine orally and 62 via nasoenteral tube. Nimodipine nasoenteral tube use was related to an increase in the regression-adjusted risk of vasospasm in 7 days (RR=2.35; 95% CI: 1.01 - 5.46) and in 21 days (RR=2.40; 95% CI: 1.05 - 5.46). **Conclusions:** This is the first study in the Brazilian (or even Latin American) context, in which the impact of the nasoenteral route of administration of nimodipine on the outcomes of vasospasm in patients with SAH. The findings suggest that the use of Nimodipine via nasoenteral tube in these patients may be associated with an increased risk of vasospasm outcome, both at 7 and 21 days of treatment. Therefore, the results should be considered in clinical practice for SAH and demonstrate the need for further studies to correlate pharmacokinetics and clinical outcomes.

Keywords: Subarachnoid hemorrhage; Nimodipine; Drug Administration Routes; Enteral nutrition; Vasospasm, Intracranial

RESUMO

Objetivo: Avaliar o papel da via de administração oral (VO) ou sonda nasoenteral (SNE) de Nimodipino no desfecho de vasoespasmo (em 7 e 21 dias) em pacientes internados com hemorragia subaracnóidea aneurismática (HSA). **Métodos:** O estudo tem delineamento de coorte retrospectiva, com dados coletados em um hospital universitário de alta complexidade de Porto Alegre. O período analisado foi entre janeiro de 2019 e janeiro de 2023. Foram incluídos pacientes maiores de 18 anos, com diagnóstico de HSA e que realizaram, no mínimo, 7 dias de tratamento com nimodipino internados. **Resultados:** Um total de 121 pacientes foram incluídos no estudo, divididos entre: 59 pacientes que utilizaram o medicamento VO e 62 que utilizaram via SNE. Foi identificado um aumento no risco ajustado por Regressão de apresentar vasoespasmo associado a administração via SNE em 7 dias (RR=2,35; IC 95%: 1,01 - 5,46) e em 21 dias (RR=2,40; IC 95%: 1,05 - 5,46). **Conclusões:** Esse é primeiro estudo dessa natureza, no contexto brasileiro ou latinoamericano, em que se comprova com dados de desfechos clínicos o impacto da via de administração de nimodipino no desfecho de vasoespasmo em pacientes com HSA. Os achados sugerem que o uso de Nimodipino via SNE nestes pacientes pode estar associado a um maior risco do desfecho de vasoespasmo, tanto em 7 como em 21 dias de tratamento. Logo, os resultados podem ser considerados na prática clínica da HSA e na condução de estudos mais aprofundados sobre o tema, que relacionem níveis séricos do fármaco e os desfechos.

Palavras-chave: Hemorragia subaracnóidea; Nimodipina; Vias de Administração de Medicamentos; Nutrição enteral; Vasoespasmo Intracraniano

Introduction

Aneurysmal Subarachnoid Hemorrhage (SAH) is a clinical condition characterized by the presence of blood within the subarachnoid space, caused by the rupture of a cerebral aneurysm. This disease typically follows a natural course involving vasoconstriction within the Central Nervous System, also referred to as vasospasm, which may lead to cerebral ischemia.[1,2] According to a recent systematic review, SAH is relatively rare, with a global incidence of 6.1 cases per 100,000 individuals, but it is a potentially fatal condition.

The only prophylactic treatment for vasospasm is the use of the drug nimodipine, in addition to neurocritical care measures.[4] A calcium channel blocker, nimodipine exerts its pharmacological action specifically on L-type receptors, which are abundantly present in the smooth muscle cells of cerebral blood vessels. By selectively inhibiting these channels, nimodipine promotes selective vasodilation of cerebral arteries, thereby increasing cerebral blood flow and oxygenation of nervous tissue. This specific mechanism of action makes nimodipine an effective therapeutic agent in neurovascular conditions, as it helps reduce the incidence of vasospasm, cerebral ischemia, and mortality.[2,4]

There are reports in the literature of reduced absorption of this drug when administered via a nasoenteric feeding tube (NFT).[5,6] These findings have biological plausibility, as the medication is available only in tablet form, and crushing this dosage form may lead to clinically significant pharmacokinetic alterations.[7]

In a recent systematic review, Geraldini et al.[9] compared the effectiveness of enteral versus intravenous administration of nimodipine in patients with subarachnoid hemorrhage (SAH). Among the ten studies analyzed, both administration routes demonstrated similar clinical outcomes, particularly regarding the incidence of vasospasm and delayed cerebral ischemia. However, the same review also concluded that its findings were limited, as seven out of the ten studies included were conducted in the 1980s. These limitations stem from small sample sizes, the evolution of clinical protocols over time, and changes in outcome definitions, all of which may have influenced the comparability and robustness of results.[9]

The studies conducted by Kronvall et al. (a randomized, unblinded clinical trial with 106 patients)[10] and Soppi et al. (also a randomized, unblinded clinical trial with 171 patients)[11] compared the use of nimodipine via enteral and intravenous routes. While Soppi's study provides details on the preparation of the suspension for administration through a nasoenteric feeding tube (NFT) in patients unable to take medications orally, Kronvall's study merely mentions that such patients received nimodipine via NFT, without describing the preparation method. Importantly, neither study specifies how many patients in the enteral group received the drug orally versus via NFT, a detail that would be critical to assess potential differences between these administration routes.

After searching for the association of the Health Sciences Descriptors (DeCS) terms "Nimodipine" and "Intracranial Vasospasm" in the PubMed, SciELO, and CAPES Journal Portal databases, it was found that no studies conducted in Brazil or Latin America have reported an increased risk of vasospasm in SAH patients receiving nimodipine via feeding tube, following tablet crushing or derivation. This finding is particularly relevant given that Brazil currently has only this pharmaceutical formulation available for commercial use and clinical administration to patients.[8]

Therefore, it is essential to evaluate the clinical outcomes of patients with subarachnoid hemorrhage (SAH) receiving nimodipine via nasoenteric tube, in comparison with those treated through the oral route. Accordingly, the objective of the present study is to assess the impact of the administration route, oral versus nasoenteric tube, of nimodipine on the incidence of vasospasm (at 7 and 21 days) in patients hospitalized with aneurysmal subarachnoid hemorrhage (SAH) at a high-complexity medical center in southern Brazil.

Methods

This is a retrospective cohort study conducted at a tertiary university hospital in southern Brazil with a total of 860 beds, including 55 intensive care unit

(ICU) beds for adults and an additional 33 intensive care beds for pediatric and neonatal patients. Data were collected retrospectively from January 1, 2019, to January 31, 2023. The study included data from patients diagnosed with subarachnoid hemorrhage (SAH), aged 18 years or older, with a minimum hospital stay of seven days and receiving nimodipine treatment. Patients diagnosed with non-aneurysmal subarachnoid hemorrhage (such as those resulting from trauma, arteriovenous malformations, bleeding disorders, or other causes) were excluded from the study.

Data Collection

Screening of eligible individuals for inclusion in the study was performed through a query extraction from the hospital's electronic medical record (EMR) database. All patient data were anonymized at the time the dataset was generated for the researchers. After selecting the patients who met the inclusion criteria, the following variables were collected: Prescription of milrinone; Performance of aneurysm clipping; Performance of decompressive craniectomy; Cranial computed tomography (CT) report; Cranial arterial CT angiography report; Transcranial Doppler ultrasound report; Length of hospital stay (in days); Length of ICU stay (in days); Prescribed diet; Clinical history and anamnesis; Previous medical history (specifically regarding alcohol use, smoking, systemic arterial hypertension, and diabetes mellitus); List of ICD codes recorded during hospitalization; Age and sex.

The outcome analyzed was the incidence of vasospasm, diagnosed through imaging examinations, specifically computed tomographic angiography (CTA) or transcranial Doppler ultrasound.

Regarding the number of days of nimodipine use and the route of administration, since the outcomes were assessed at 7-day and 21-day intervals, and some patients switched administration routes during the same treatment period, patients were categorized into either the oral or nasoenteric tube (NFT) group based on the predominant route used. In other words, if a patient received nimodipine via nasoenteric tube for 4 days and orally for 3 days within the 7-day assessment period, they were classified in the NFT group. Conversely, if a patient used nimodipine orally for 11 days and via NFT for 10 days within the 21-day period, they were classified in the oral administration group.

Statistical Analysis

The sample size calculation indicated the need for at least 98 participants (29 in the nasoenteric tube group and 69 in the oral group) to test for a potential statistical difference in the incidence of vasospasm between the two administration routes. This calculation was based on the results of a previous study that employed a similar methodology.[6,12]

The statistical analysis included the evaluation of frequencies, means, and standard deviations for quantitative variables, with comparisons between groups performed using the Student's *t*-test. Nominal variables were expressed as percentages and compared using the chi-square test. For the incidence of vasospasm, a Poisson regression analysis was conducted to calculate the relative risk, adjusting the results for the clinical characteristics of the studied condition. The relative risk parameter was chosen as the most appropriate for this type of study (retrospective cohort), and the Poisson model was selected for its ability to account for the simultaneous effects of multiple factors influencing outcomes.

Prior to the regression analysis, a bivariate analysis of the vasospasm outcome was performed in relation to the study variables (hypertension, diabetes, obesity, sex, age, decompressive craniectomy, aneurysm clipping, drug administration route, smoking, and alcohol use) using simple Poisson regression, assessed individually for each variable.

After the bivariate analysis, only the variables that reached statistical significance at the 10% level ($p \leq 0.10$) were included in a preliminary regression model, with the goal of selecting those with the greatest impact on the vasospasm outcome for inclusion in the multivariate regression model. Variables that did not achieve statistical significance ($p > 0.05$) were subsequently removed, resulting in a final model comprising two variables.

The statistical analysis of the data was performed using the SPSS (Statistical Package for the Social Sciences) software, version 29.0.1.

Ethical Aspects

The study was submitted to and approved by the Institutional Research Ethics Committee of the institution where it was conducted, under the protocol number CAAE: 66395822.7.0000.5327 (approval statement No. 6.011.960), in full compliance with all ethical and regulatory requirements for its execution.

Results

The screening of eligible patients identified a total of 153 individuals, with 121 participants ultimately included in the study (Figure 1), thus meeting the sample size required for the proposed methodology. The baseline characteristics of the patients included in the study are presented in Table 1.

Figure 1. Sample Selection Flowchart

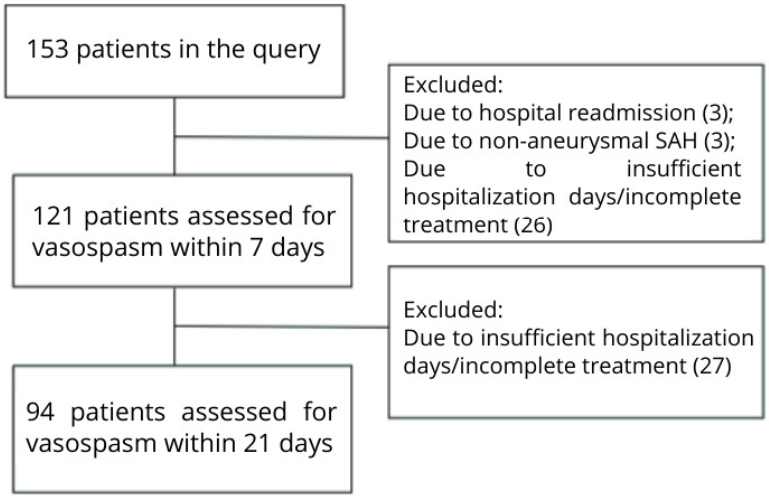

Table 1. Characteristics of Patients with Subarachnoid Hemorrhage (SAH) Using Nimodipine (Oral or Nasoenteric Route) in a Tertiary Care Hospital from January 2019 to January 2023.

	PO (n=59)	NTE (n=62)	p-Value
Age[a]	54 ± 10	59 ± 11	0.03
Female, Sex[b]	42 (71.2%)	49 (79.0%)	0.32
Length of Stay[a]	19 ± 9	30 ± 21	<0.01
Days in the Intensive Care Unit (ICU)[a]	11 ± 10	26 ± 28	<0.01
Descompressive Craniectomy Procedure[b]	0 (0%)	8 (12.9%)	<0.01
Aneurysm Clipping Procedure[b]	20 (33.8%)	19 (30.6%)	0.34
Use of the drug milrinone[b]	5 (8.5%)	15 (24.2%)	0.02
Previous Hypertension[b]	19 (32.2%)	21 (33.8%)	0.85
Diabetes[b]	3 (5%)	2 (3%)	0.61
Smoking[b]	-	-	0.15
Non smoker	46 (77,9%)	54 (87,1%)	-
Current smoker	10 (16,9%)	8 (12,9%)	-
Former smoker	3 (5%)	0 (0%)	-
Alcohol user[b]	-	-	0,62
Non-drinker	55 (93,2%)	57 (91,9%)	-
Alcohol user	4 (6,8%)	4 (6,5%)	-
Former alcohol user	0 (0%)	1 (1,6%)	-
Obesity[b]	1 (1,6%)	3 (4,8%)	0,33

Legend: a - quantitative variables presented as mean and corresponding stardand deviation; b - nominal variables presented as absolute numbers and percentagens (n, %). SAH: Aneurysmal Subarachnoid Hemorrhage; VO: Oral route; NTEE: Nasorenteral tube.

Table 2 presents the incidence of vasospasm in the study groups, showing a statistically significant difference between patients who received nimodipine via nasoenteric tube and those who received it orally, both at 7 days and 21 days.

The multivariate Poisson regression analysis allowed for the exclusion of variables that did not show a significant effect on the incidence of vasospasm at 7 days, namely: diabetes, age, sex, decompressive craniectomy, milrinone use, smoking, alcohol use, and obesity.

The variables aneurysm clipping and history of hypertension were found to be correlated with the vasospasm outcome, as was the route of drug administration. The results demonstrated that even after parameter adjustment (accounting for other factors influencing vasospasm incidence), the route of administration remained statistically significantly associated with the vasospasm outcome, as shown in Table 3.

In the multivariate regression analysis for data collected at 21 days, the variables that reached statistical significance and were included in the final model were: patient sex, aneurysm clipping, and the route of drug administration. Once again, even after parameter adjustment to account for potential confounding factors that could influence the incidence of vasospasm, the route of administration remained statistically significant (Table 4).

During the study period, 26 patients with SAH (out of a total of 121 analyzed) died, resulting in an in-hospital mortality rate of 21.5% for the study population.

Table 2. Incidence of Vasospasm at 7 and 21 Days After Initiation of Nimodipine in Patients with Subarachnoid Hemorrhage (SAH)

	Oral Administration	Administration via SNE	*p*-Value
7 days after the initation of Nimodipine	Total pela Via Oral (n=59)	Total pela Via Sonda (n=62)	
Presence of Vasoespasm (n;%)	6 (10.2%)	15 (24.2%)	0.04
21 days after the initiation of Nimodipine	Total pela Via Oral: (n=47)	Total pela Via Sonda (n=47)	-
Presence of Vasoespasm (n;%)	6 (12.8%)	16 (34%)	0.02

SAH: Aneurysmal Subarachnoid Hemorrhage; NTE: Nasoenteric Tube.

Table 3. Poisson Regression Results for Vasospasm Outcome Compared with the Route of Nimodipine Administration After 7 Days of Treatment

	Relative Risk	Confidence Interval (95%)	*p*-Value
Use of nimodipine via NTE	2.35	1.01 - 5.46	0.05
Aneurysm Clipping	2.80	1.34 - 5.86	<0.01
Previously Hypertension	2.45	1.18 - 5.08	0.02

NTE: Nascoenteric Tube

Table 4. Poisson Regression Results for Vasospasm Outcome Compared with the Route of Nimodipine Administration After 21 Days of Treatment

	Risco relativo	Confidence interval	*p*-Value
UUse of nimodipine via NTE	2.40	1.05 - 5.46	0.04
Aneurysm Clipping	2.01	0.983 - 4.11	0.06
Sex (Female)	5.46	0.840 - 5.48	0.08

NTE: Nascoenteric Tube

Discussion

This is the first study, within both the Brazilian and Latin American contexts, to analyze the impact of the route of nimodipine administration on the clinical outcomes of patients with post-subarachnoid hemorrhage (SAH) in countries where the intravenous formulation of the drug is not available for use. In this study, nimodipine administration via nasoenteric feeding tube was significantly associated with an increased risk of developing vasospasm, the primary outcome evaluated. This association remained statistically significant even after multivariate adjustment using Poisson regression, which accounted for all previously mentioned clinical and demographic characteristics of the study sample.

The study sample had a mean age above 50 years and was predominantly female, findings that are consistent with recent literature.[1,3] Most of the patient characteristics in each group (nasoenteric tube – NFT and oral route – OR) were similar, as indicated by the p-values presented in Table 1. Therefore, the study groups exhibited comparable baseline characteristics, which are expected in patients with subarachnoid hemorrhage (SAH), supporting the validity of the comparative analyses performed.

However, some factors showed statistically significant differences between the nasoenteric tube (NFT) and oral (OR) groups. These included age, length of hospital stay, length of ICU stay, performance of decompressive craniectomy, and use of milrinone. Notably, the decompressive craniectomy procedure was performed exclusively among patients in the NFT group, suggesting that this subgroup comprised patients with greater clinical severity.

The increased relative risk of developing vasospasm among patients treated with nimodipine via nasoenteric tube (NFT) may be partially explained by factors previously identified in the sample characterization. Notably, only patients receiving the calcium channel blocker through NFT underwent decompressive craniectomy, a procedure that is typically an indicator of poorer prognosis and greater clinical severity in cases of subarachnoid hemorrhage. However, it is also not possible to rule out the influence of variable drug absorption when comparing nasoenteric versus oral administration.[5,6,7] This consideration is reinforced by the fact that the results shown in Tables 3 and 4 were adjusted for other clinical factors through Poisson regression, and because proper nimodipine use is well established to reduce the incidence of vasospasm.[2] Furthermore, an increased risk of vasospasm in patients receiving nimodipine via nasoenteric tube has already been reported in a Canadian study.[6] The biological hypothesis underlying this finding relates to the extremely variable absorption observed when crushed tablets are administered through a feeding tube, with a pharmacokinetic study demonstrating that some patients exhibited undetectable serum concentrations of nimodipine, while others had levels up to twice as high as those in the same group.[5]

Regarding the in-hospital mortality rate observed (21.5%), the value is similar to that reported in the literature,[13,14] considering that the referenced data come from clinical trials conducted in specialized neurological centers, comparable to the institution where the present study was performed.

Study Limitations

This study has several limitations. The retrospective data collection relied on previous patient medical records, which is an inherent limitation of retrospective cohort studies. Additionally, to better understand the correlation between administration routes and clinical outcomes, it would be essential to include the assessment of pharmacokinetic parameters to clarify the drug's behavior in the body. Such pharmacokinetic evaluation was not performed in the present study, but its absence highlights an important direction for future research to complement and expand upon the findings reported here.

Conclusion

The results of this study demonstrated that when administered via nasoenteric tube, nimodipine is associated with a higher adjusted relative risk of vasospasm occurrence in patients with aneurysmal subarachnoid hemorrhage (SAH), at both 7 and 21 days of treatment.

These results provide original data within the Brazilian context, where the intravenous formulation of nimodipine is not available, unlike in other countries. This clinical adaptation commonly employed in daily hospital practice underscores the need for pharmacokinetic studies linked to clinical outcomes, in order to improve the quality of care provided to patients with aneurysmal subarachnoid hemorrhage (SAH).

Authors' Contributions

GC: Data curation, formal analysis, investigation, methodology, project administration, visualization, and writing, review and editing of both the original draft and the final version of the manuscript; JRCG: Data curation, formal analysis, methodology, and writing, review and editing of both the original draft and the final version of the manuscript; VZ: Conceptualization, supervision, and writing, review and editing of both the original draft and the final version of the manuscript; LE: Supervision, methodology, visualization, and writing, review and editing of both the original draft and the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Responsible Reviewers

Lindemberg Assunção and Juliana Machado

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